THERAPEUTIC AGENTS USEFUL FOR TREATING PAIN

This application claims the benefit of U.S. Provisional Application No. 60/391,962, filed June 28, 2002; U.S. Provisional Application No. 60/411,030, filed September 17, 2002; U.S. Provisional Application No. 60/413,148, filed September 25, 2002; and U.S. Provisional Application No. 60/416,582, filed October 8, 2002, each of which is incorporated herein by reference in its entirety.

1. FIELD OF THE INVENTION

The present invention relates to Cyanoiminopiperazine Compounds, compositions comprising an effective amount of a Cyanoiminopiperazine Compound and methods for treating or preventing pain, urinary incontinence (UI), an ulcer, inflammatory-bowel disease (IBD), irritable-bowel syndrome (IBS), an addictive disorder, Parkinson's disease, parkinsonism, anxiety, epilepsy, stroke, a seizure, a pruritic condition, psychosis, a cognitive disorder, a memory deficit, restricted brain function, Huntington's chorea, amyotrophic lateral sclerosis (ALS), dementia, retinopathy, a muscle spasm, a migraine, vomiting, dyskinesia or depression, comprising administering to an animal in need thereof an effective amount of a Cyanoiminopiperazine Compound.

2. BACKGROUND OF THE INVENTION

Pain is the most common symptom for which patients seek medical advice and treatment. Pain can be acute or chronic. While acute pain is usually self-limited, chronic pain persists for 3 months or longer and can lead to significant changes in a patient's personality, lifestyle, functional ability and overall quality of life (K.M. Foley, *Pain, in Cecil Textbook of Medicine* 100-107 (J.C. Bennett and F. Plum eds., 20th ed. 1996)).

Moreover, chronic pain can be classified as either nociceptive or neuropathic. Nociceptive pain includes tissue injury-induced pain and inflammatory pain such as that associated with arthritis. Neuropathic pain is caused by damage to the peripheral or cental nervous system and is maintained by aberrant somatosensory processing. There is a large body of evidence relating activity at both Group I metabotropic glutamate receptors, i.e., metabotropic glutamate receptor 1 ("mGluR1") and metabotropic glutamate receptor 5 ("mGluR5") (M.E. Fundytus, *CNS Drugs* 15:29-58 (2001)), and vanilloid receptors ("VR1")

(V. Di Marzo *et al.*, *Current Opinion in Neurobiology* 12:372-379 (2002)) to pain processing. Inhibiting mGluR1 or mGluR5 reduces pain, as shown by *in vivo* treatment with antibodies selective for either mGluR1 or mGluR5, where neuropathic pain in rats was attenuated (M.E. Fundytus *et al.*, *NeuroReport* 9:731-735 (1998)). It has also been shown that antisense oligonucleotide knockdown of mGluR1 alleviates both neuropathic and inflammatory pain (M.E. Fundytus *et al.*, *British Journal of Pharmacology* 132:354-367 (2001); M.E. Fundytus *et al.*, *Pharmacology, Biochemsitry & Behavior* 73:401-410 (2002)). Small molecule antagonists for mGluR5-attenuated pain in *in vivo* animal models are disclosed in, e.g., K. Walker *et al.*, *Neuropharmacology* 40:1-9 (2000) and A. Dogrul *et al.*, *Neuroscience Letters* 292:115-118 (2000)).

Nociceptive pain has been traditionally managed by administering non-opioid analgesics, such as acetylsalicylic acid, choline magnesium trisalicylate, acetaminophen, ibuprofen, fenoprofen, diflusinal, and naproxen; or opioid analgesics, including morphine, hydromorphone, methadone, levorphanol, fentanyl, oxycodone, and oxymorphone. *Id.* In addition to the above-listed treatments, neuropathic pain, which can be difficult to treat, has also been treated with anti-epileptics (e.g. gabapentin, carbamazepine, valproic acid, topiramate, phenytoin), NMDA antagonists (e.g. ketamine, dextromethorphan), topical lidocaine (for post-herpetic neuralgia), and tricyclic antidepressants (e.g. fluoxetine, sertraline and amitriptyline).

UI is uncontrollable urination, generally caused by bladder-detrusor-muscle instability. UI affects people of all ages and levels of physical health, both in health care settings and in the community at large. At present, UI afflicts 15-30% of elderly people living at home, one-third of those living in acute-care settings, and at least one-half of those living in long-term care institutions (R.M. Resnick, *Lancet* 346:94 (1995)). Persons having UI are predisposed to also having urinary-tract infections, pressure ulcers, perineal rashes and urosepsis. Psychosocially, UI is associated with embarrassment, social stigmatization, depression and a risk of institutionalization (Herzo *et al.*, *Annu. Rev. Gerontol. Geriatr.* 9:74 (1989)). Economically, the costs of UI are great; in the United States alone, health-care costs associated with UI are over $15 billion per annum.

Physiologic bladder contraction results in large part from acetylcholine-induced stimulation of post-ganglionic muscarinic-receptor sites on bladder smooth muscle.

Treatments for UI include the administration of drugs having bladder-relaxant properties, which help to control bladder-detrusor-muscle overactivity. For example, anticholinergics such as propantheline bromide and glycopyrrolate, and combinations of smooth-muscle relaxants such as a combination of racemic oxybutynin and dicyclomine or an anticholinergic, have been used to treat UI (*See, e.g.*, A.J. Wein, *Urol. Clin. N. Am.* 22:557-577 (1995); Levin *et al.*, *J. Urol.* 128:396-398 (1982); Cooke *et al.*, *S. Afr. Med. J.* 63:3 (1983); R.K. Mirakhur *et al.*, *Anaesthesia* 38:1195-1204 (1983)). These drugs are not effective, however, in all patients having uninhibited bladder contractions. Administration of anticholinergic medications represent the mainstay of this type of treatment.

None of the existing commercial drug treatments for UI, however, has achieved complete success in all classes of UI patients, nor has treatment occurred without significant adverse side effects. For example, drowsiness, dry mouth, constipation, blurred vision, headaches, tachycardia, and cardiac arrhythmia, which are related to the anticholinergic activity of traditional anti-UI drugs, can occur frequently and adversely affect patient compliance. Yet despite the prevalence of unwanted anticholinergic effects in many patients, anticholinergic drugs are currently prescribed for patients having UI. *The Merck Manual of Medical Information* 631-634 (R. Berkow ed., 1997).

Ulcers are sores occurring where the lining of the digestive tract has been eroded by stomach acids or digestive juices. The sores are typically well-defined round or oval lesions primarily occurring in the stomach and duodenum. About 1 in 10 people develop an ulcer. Ulcers develop as a result of an imbalance between acid-secretory factors, also known as "aggressive factors," such as stomach acid, pepsin, and *Helicobacter pylori* infection, and local mucosal-protective factors, such as secretion of bicarbonate, mucus, and prostaglandins.

Treatment of ulcers typically involves reducing or inhibiting the aggressive factors. For example, antacids such as aluminum hydroxide, magnesium hydroxide, sodium bicarbonate, and calcium bicarbonate can be used to neutralize stomach acids. Antacids, however, can cause alkalosis, leading to nausea, headache, and weakness. Antacids can also interfere with the absorption of other drugs into the blood stream and cause diarrhea.

H_2 antagonists, such as cimetidine, ranitidine, famotidine, and nizatidine, are also used to treat ulcers. H_2 antagonists promote ulcer healing by reducing gastric acid and

digestive-enzyme secretion elicited by histamine and other H_2 agonists in the stomach and duodenum. H_2 antagonists, however, can cause breast enlargement and impotence in men, mental changes (especially in the elderly), headache, dizziness, nausea, myalgia, diarrhea, rash, and fever.

H^+, K^+ - ATPase inhibitors such as omeprazole and lansoprazole are also used to treat ulcers. H^+, K^+ - ATPase inhibitors inhibit the production of enzymes used by the stomach to secrete acid. Side effects associated with H^+, K^+ - ATPase inhibitors include nausea, diarrhea, abdominal colic, headache, dizziness, somnolence, skin rashes, and transient elevations of plasma activities of aminotransferases.

Sucraflate is also used to treat ulcers. Sucraflate adheres to epithelial cells and is believed to form a protective coating at the base of an ulcer to promote healing. Sucraflate, however, can cause constipation, dry mouth, and interfere with the absorption of other drugs.

Antibiotics are used when *Helicobacter pylori* is the underlying cause of the ulcer. Often antibiotic therapy is coupled with the administration of bismuth compounds such as bismuth subsalicylate and colloidal bismuth citrate. The bismuth compounds are believed to enhance secretion of mucous and HCO_3^-, inhibit pepsin activity, and act as an antibacterial against *H. pylori*. Ingestion of bismuth compounds, however, can lead to elevated plasma concentrations of Bi^{+3} and can interfere with the absorption of other drugs.

Prostaglandin analogues, such as misoprostal, inhibit secretion of acid and stimulate the secretion of mucous and bicarbonate and are also used to treat ulcers, especially ulcers in patients who require nonsteroidal anti-inflammatory drugs. Effective oral doses of prostaglandin analogues, however, can cause diarrhea and abdominal cramping. In addition, some prostaglandin analogues are abortifacients.

Carbenoxolone, a mineral corticoid, can also be used to treat ulcers. Carbenoxolone appears to alter the composition and quantity of mucous, thereby enhancing the mucosal barrier. Carbenoxolone, however, can lead to Na^+ and fluid retention, hypertension, hypokalemia, and impaired glucose tolerance.

Muscarinic cholinergic antagonists such as pirenzapine and telenzapine can also be used to reduce acid secretion and treat ulcers. Side effects of muscarinic cholinergic antagonists include dry mouth, blurred vision, and constipation. *The Merck Manual of Medical Information* 496-500 (R. Berkow ed., 1997) and *Goodman and Gilman's The*

Pharmacological Basis of Therapeutics 901-915 (J. Hardman and L. Limbird eds., 9th ed. 1996).

IBD is a chronic disorder in which the bowel becomes inflamed, often causing recurring abdominal cramps and diarrhea. The two types of IBD are Crohn's disease and ulcerative colitis.

Crohn's disease, which can include regional enteritis, granulomatous ileitis, and ileocolitis, is a chronic inflammation of the intestinal wall. Crohn's disease occurs equally in both sexes and is more common in Jews of eastern-European ancestry. Most cases of Crohn's disease begin before age 30 and the majority start between the ages of 14 and 24. The disease typically affects the full thickness of the intestinal wall. Generally the disease affects the lowest portion of the small intestine (ileum) and the large intestine, but can occur in any part of the digestive tract.

Early symptoms of Crohn's disease are chronic diarrhea, crampy abdominal pain, fever, loss of appetite, and weight loss. Complications associated with Crohn's disease include the development of intestinal obstructions, abnormal connecting channels (fistulas), and abscesses. The risk of cancer of the large intestine is increased in people who have Crohn's disease. Often Crohn's disease is associated with other disorders such as gallstones, inadequate absorption of nutrients, amyloidosis, arthritis, episcleritis, aphthous stomatitis, erythema nodosum, pyoderma gangrenosum, ankylosing spondylitis, sacroilitis, uveitis, and primary sclerosing cholangitis. There is no known cure for Crohn's disease.

Cramps and diarrhea, side effects associated with Crohn's disease, can be relieved by anticholinergic drugs, diphenoxylate, loperamide, deodorized opium tincture, or codeine. Generally, the drug is taken orally before a meal.

Broad-spectrum antibiotics are often administered to treat the symptoms of Crohn's disease. The antibiotic metronidazole is often administered when the disease affects the large intestine or causes abscesses and fistulas around the anus. Long-term use of metronidazole, however, can damage nerves, resulting in pins-and-needles sensations in the arms and legs. Sulfasalazine and chemically related drugs can suppress mild inflammation, especially in the large intestine. These drugs, however, are less effective in sudden, severe flare-ups. Corticosteroids, such as prednisone, reduce fever and diarrhea and relieve abdominal pain and tenderness. Long-term corticosteroid therapy, however, invariably results

in serious side effects such as high blood-sugar levels, increased risk of infection, osteoporosis, water retention, and fragility of the skin. Drugs such as azathioprine and mercaptourine can compromise the immune system and are often effective for Crohn's disease in patients that do not respond to other drugs. These drugs, however, usually need 3 to 6 months before they produce benefits and can cause serious side effects such as allergy, pancreatitis, and low white-blood-cell count.

When Crohn's disease causes the intestine to be obstructed or when abscesses or fistulas do not heal, surgery can be necessary to remove diseased sections of the intestine. Surgery, however, does not cure the disease, and inflammation tends to recur where the intestine is rejoined. In almost half of the cases a second operation is needed. *The Merck Manual of Medical Information* 528-530 (R. Berkow ed., 1997).

Ulcerative colitis is a chronic disease in which the large intestine becomes inflamed and ulcerated, leading to episodes of bloody diarrhea, abdominal cramps, and fever. Ulcerative colitis usually begins between ages 15 and 30; however, a small group of people have their first attack between ages 50 and 70. Unlike Crohn's disease, ulcerative colitis never affects the small intestine and does not affect the full thickness of the intestine. The disease usually begins in the rectum and the sigmoid colon and eventually spreads partially or completely through out the large intestine. The cause of ulcerative colitis is unknown.

Treatment of ulcerative colitis is directed to controlling inflammation, reducing symptoms, and replacing lost fluids and nutrients. Anticholinergic drugs and low doses of diphenoxylate or loperamide are administered for treating mild diarrhea. For more intense diarrhea higher doses of diphenoxylate or loperamide, or deodorized opium tincture or codeine are administered. Sulfasalazine, olsalazie, prednisone, or mesalamine can be used to reduce inflammation. Azathioprine and mercaptopurine have been used to maintain remissions in ulcerative-colitis patients who would otherwise need long-term corticosteroid treatment. In severe cases of ulcerative colitis the patient is hospitalized and given corticosteroids intravenously. People with severe rectal bleeding can require transfusions and intravenous fluids. If toxic colitis develops and treatments fail, surgery to remove the large intestine can be necessary. Non-emergency surgery can be performed if cancer is diagnosed, precancerous legions are detected, or unremitting chronic disease would otherwise make the person an invalid or dependent on high doses of corticosteroids. Complete removal of the

large intestine and rectum permanently cures ulcerative colitis. *The Merck Manual of Medical Information* 530-532 (R. Berkow ed., 1997) and *Goodman and Gilman's The Pharmacological Basis of Therapeutics* (J. Hardman and L. Limbird eds., 9th ed. 1996).

IBS is a disorder of motility of the entire gastrointestinal tract, causing abdominal pain, constipation, and/or diarrhea. IBS affects three-times more women than men. In IBS stimuli such as stress, diet, drugs, hormones, or irritants can cause the gastrointestinal tract to contract abnormally. During an episode of IBS contractions of the gastrointestinal tract become stronger and more frequent, resulting in the rapid transit of food and feces through the small intestine, often leading to diarrhea. Cramps result from the strong contractions of the large intestine and increased sensitivity of pain receptors in the large intestine.

There are two major types of IBS. The first type, spastic-colon type, is commonly triggered by eating, and usually produces periodic constipation and diarrhea with pain. Mucous often appears in the stool. The pain can come in bouts of continuous dull aching pain or cramps, usually in the lower abdomen. The person suffering from spastic-colon type IBS can also experience bloating, gas, nausea, headache, fatigue, depression, anxiety, and difficulty concentrating. The second type of IBS usually produces painless diarrhea or constipation. The diarrhea can begin suddenly and with extreme urgency. Often the diarrhea occurs soon after a meal and can sometimes occur immediately upon awakening.

Treatment of IBS typically involves modification of an IBS-patient's diet. Often it is recommended that an IBS patient avoid beans, cabbage, sorbitol, and fructose. A low-fat, high-fiber diet can also help some IBS patients. Regular physical activity can also help keep the gastrointestinal tract functioning properly. Drugs such as propantheline that slow the function of the gastrointestinal tract are generally not effective for treating IBS. Antidiarrheal drugs, such as diphenoxylate and loperamide, help with diarrhea. *The Merck Manual of Medical Information* 525-526 (R. Berkow ed., 1997).

Many drugs can cause physical and/or psychological addiction. Those most well known types of these drugs include opiates, such as heroin, opium, and morphine; sympathomimetics, including cocaine and amphetamines; sedative-hypnotics, including alcohol, benzodiazepines and barbiturates; and nicotine, which has effects similar to opioids and sympathomimetics. Drug addiction is characterized by a craving or compulsion for

taking the drug and an inability to limit its intake. Additionally, drug dependence is associated with drug tolerance, the loss of effect of the drug following repeated administration, and withdrawal, the appearance of physical and behavioral symptoms when the drug is not consumed. Sensitization occurs if repeated administration of a drug leads to an increased response to each dose. Tolerance, sensitization, and withdrawal are phenomena evidencing a change in the central nervous system resulting from continued use of the drug. This change can motivate the addicted individual to continue consuming the drug despite serious social, legal, physical and/or professional consequences. (*See, e.g.*, U.S. Patent No. 6,109,269 to Rise *et al.*).

Certain pharmaceutical agents have been administered for treating addiction. U.S. Patent No. 5,556,838 to Mayer *et al.* discloses the use of nontoxic NMDA-blocking agents co-administered with an addictive substance to prevent the development of tolerance or withdrawal symptoms. U.S. Patent No. 5,574,052 to Rose *et al.* discloses co-administration of an addictive substance with an antagonist to partially block the pharmacological effects of the substance. U.S. Patent No. 5,075,341 to Mendelson *et al.* discloses the use of a mixed opiate agonist/antagonist to treat cocaine and opiate addiction. U.S. Patent No. 5,232,934 to Downs discloses administration of 3-phenoxypyridine to treat addiction. U.S. Patents No. 5,039,680 and 5,198,459 to Imperato *et al.* disclose using a serotonin antagonist to treat chemical addiction. U.S. Patent No. 5,556,837 to Nestler et. al. discloses infusing BDNF or NT-4 growth factors to inhibit or reverse neurological adaptive changes that correlate with behavioral changes in an addicted individual. U.S. Patent. No. 5,762,925 to Sagan discloses implanting encapsulated adrenal medullary cells into an animal's central nervous system to inhibit the development of opioid intolerance. U.S. Patent No. 6,204,284 to Beer *et al.* discloses racemic (±)-1-(3,4-dichlorophenyl)-3-azabicyclo[3.1.0]hexane for use in the prevention or relief of a withdrawal syndrome resulting from addiction to drugs and for the treatment of chemical dependencies.

Parkinson's disease is a clinical syndrome comprising bradykinesia (slowness and poverty of movement), muscular rigidity, resting tremor (which usually abates during voluntary movement), and an impairment of postural balance leading to disturbance of gait and falling. The features of Parkinson's disease are a loss of pigmented, dopaminergic neurons of the substantia nigra pars compacta and the appearance of intracellular inclusions

known as Lewy bodies (*Goodman and Gillman's The Pharmaceutical Basis of Therapeutics* 506 (9th ed. 1996)). Without treatment, Parkinson's disease progresses to a rigid akinetic state in which patients are incapable of caring for themselves. Death frequently results from complications of immobility, including aspiration pneumonia or pulmonary embolism. Drugs commonly used for the treatment of Parkinson's disease include carbidopa/levodopa, pergolide, bromocriptine, selegiline, amantadine, and trihexyphenidyl hydrochloride. There remains, however, a need for drugs useful for the treatment of Parkinson's disease and having an improved therapeutic profile.

Anxiety is a fear, apprehension, or dread of impending danger often accompanied by restlessness, tension, tachycardia, and dyspnea. Other symptoms commonly associated with anxiety include depression, especially accompanied with dysthymic disorder (chronic "neurotic" depression); panic disorder; agoraphobia and other specific phobias; eating disorders; and many personality disorders. Often anxiety is unattached to a clearly identified treatable primary illness. If a primary illness is found, however, it can be desirable to deal with the anxiety at the same time as the primary illness.

Currently, benzodiazepines are the most commonly used anti-anxiety agents for generalized anxiety disorder. Benzodiazepines, however, carry the risk of producing impairment of cognition and skilled motor functions, particularly in the elderly, which can result in confusion, delerium, and falls with fractures. Sedatives are also commonly prescribed for treating anxiety. The azapirones, such as buspirone, are also used to treat moderate anxiety. The azapirones, however, are less useful for treating severe anxiety accompanied with panic attacks.

Epilepsy is a disorder characterized by the tendency to have recurring seizures. The etiology commonly consists of lesions in some part of the cortex, such as a tumor; developmental malformation; or damage due to trauma or stroke. In some cases the etiology is genetic. An epileptic seizure can be triggered by repetitive sounds, flashing lights, video games, or touching certain parts of the body. Epilepsy is typically treated with anti-seizure drugs. In epilepsy cases, where anti-seizure drugs are ineffective, and the defect in the brain is isolated to a small area of the brain, surgical removal of that part of the brain can be helpful in alleviating the seizures. In patients who have several sources for the seizures or who have

seizures that spread quickly to all parts of the brain, surgical removal of the nerve fibers that connect the two sides of the brain can be helpful.

Examples of drugs for treating a seizure and epilepsy include carbamazepine, ethosuximide, gabapentin, lamotrignine, phenobarbital, phenytoin, primidone, valproic acid, trimethadione, bemzodiaepines, γ-vinyl GABA, acetazolamide, and felbamate. Anti-seizure drugs, however, can have side effects such as drowsiness; hyperactivity; hallucinations; inability to concentrate; central and peripheral nervous system toxicity, such as nystagmus, ataxia, diplopia, and vertigo; gingival hyperplasia; gastrointestinal disturbances such as nausea, vomiting, epigastric pain, and anorexia; endocrine effects such as inhibition of antidiuretic hormone, hyperglycemia, glycosuria, osteomalacia; and hypersensitivity such as scarlatiniform rash, morbilliform rash, Stevens-Johnson syndrome, systemic lupus erythematosus, and hepatic necrosis; and hematological reactions such as red-cell aplasia, agranulocytosis, thrombocytopenia, aplastic anemia, and megaloblastic anemia. *The Merck Manual of Medical Information* 345-350 (R. Berkow ed., 1997).

A seizure is the result of abnormal electrical discharge in the brain. The discharge can involve a small area of the brain and lead to the person only noticing an odd taste or smell or it can involve a large area of the brain and lead to convulsions, *i.e.*, a seizure that causes jerking and spasms of the muscles throughout the body. Convulsions can also result in brief attacks of altered consciousness and loss of consciousness, muscle control, or bladder control. A seizures is often preceded by auras, *i.e.*, unusual sensations of smell, taste, or vision or an intense feeling that a seizure is about to begin. A seizure typically lasts for about 2 to 5 minutes. When the seizure ends the person can have headache, sore muscles, unusual sensations, confusion, and profound fatigue (postictal state). Usually the person cannot remember what happened during the seizure.

A stroke or cerebrovascular accident, is the death of brain tissue (cerebral infarction) resulting from the lack of blood flow and insufficient oxygen to the brain. A stroke can be either ischemic or hemorrhagic. In an ischemic stroke, blood supply to the brain is cut off because of atherosclerosis or a blood clot that has blocked a blood vessel. In a hemorrhagic stroke, a blood vessel bursts preventing normal blood flow and allowing blood to leak into an area of the brain and destroying it. Most strokes develop rapidly and cause brain damage within minutes. In some cases, however, strokes can continue to worsen for

several hours or days. Symptoms of strokes vary depending on what part of the brain is effected. Symptoms include loss or abnormal sensations in an arm or leg or one side of the body, weakness or paralysis of an arm or leg or one side of the body, partial loss of vison or hearing, double vision, dizziness, slurred speech, difficulty in thinking of the appropriate word or saying it, inability to recognize parts of the body, unusual movements, loss of bladder control, imbalance, and falling, and fainting. The symptoms can be permanent and can be associated with coma or stupor. Strokes can cause edema or swelling of the brain which can further damage brain tissue. For persons suffering from a stroke, intensive rehabilitation can help overcome the disability caused by impairment of brain tissue. Rehabilitation trains other parts of the brain to assume the tasks previously performed by the damaged part.

Examples of drugs for treating strokes include anticoagulants such as heparin, drugs that break up clots such as streptokinase or tissue plasminogen activator, and drugs that reduce swelling such as mannitol or corticosteroids. *The Merck Manual of Medical Information* 352-355 (R. Berkow ed., 1997).

Pruritus is an unpleasant sensation that prompts scratching. Pruritus can be attributed to dry skin, scabies, dermatitis, herpetiformis, atopic dermatitis, *pruritus vulvae et ani*, miliaria, insect bites, pediculosis, contact dermatitis, drug reactions, urticaria, urticarial eruptions of pregnancy, psoriasis, lichen planus, lichen simplex chronicus, exfoliative dermatitis, folliculitis, bullous pemphigoid, and fiberglass dermatitis. Conventionally, pruritus is treated by phototherapy with ultraviolet B or PUVA or with therapeutic agents such as naltrexone, nalmefene, danazol, tricyclics, and antidepressants.

Selective antagonists of the metabotropic glutamate receptor 5 ("mGluR5") have been shown to exert analgesic activity in *in vivo* animal models (K. Walker *et al.*, *Neuropharmacology* 40:1-9 (2000) and A. Dogrul *et al.*, *Neuroscience Letters*, 292(2):115-118 (2000)).

Selective antagonists of the mGluR5 receptor have also been shown to exert anxiolytic and anti-depressant activity in *in vivo* animal models (E. Tatarczynska *et al.*, *Br. J. Pharmacol.* 132(7):1423-1430 (2001) and P.J.M. Will *et al.*, *Trends in Pharmacological Sciences* 22(7):331-37 (2001)).

Selective antagonists of the mGluR5 receptor have also been shown to exert anti-Parkinson activity *in vivo* (K. J. Ossowska *et al.*, *Neuropharmacology* 41(4):413-20 (2001) and P.J.M. Will *et al.*, *Trends in Pharmacological Sciences* 22(7):331-37 (2001)).

Selective antagonists of the mGluR5 receptor have also been shown to exert anti-dependence activity *in vivo* (C. Chiamulera *et al.*, *Nature Neuroscience* 4(9):873-74 (2001)).

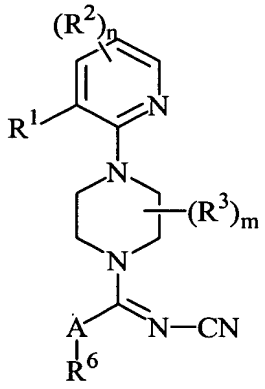
International publication no. WO 02/16318 discloses a class of N-cyanoimines allegedly useful for treating a acute pain, urinary bladder hypersensitiveness, an ulcer, IBD, and IBS.

There remains, however, a clear need in the art for new drugs useful for treating or preventing pain, UI, an ulcer, IBD, IBS, an addictive disorder, Parkinson's disease, parkinsonism, anxiety, epilepsy, stroke, a seizure, a pruritic condition, psychosis, a cognitive disorder, a memory deficit, restricted brain function, Huntington's chorea, ALS, dementia, retinopathy, a muscle spasm, a migraine, vomiting, dyskinesia, or depression.

Citation of any reference in Section 2 of this application is not to be construed as an admission that such reference is prior art to the present application

3. SUMMARY OF THE INVENTION

The present invention encompasses compounds having the formula (I):



(I)

and pharmaceutically acceptable salts thereof, wherein:

A is $-NR^4-$, -O-, or -S-;

R^1 is -halo, $-CH_3$, $-NO_2$, -CN, -OH, $-OCH_3$, $-NH_2$, $-C(halo)_3$, $-CH(halo)_2$, or

$-CH_2(halo)$;

each R^2 is independently:

(a) -halo, -CN, -OH, $-NO_2$, or $-NH_2$;

(b) $-(C_1-C_{10})$alkyl, $-(C_2-C_{10})$alkenyl, $-(C_2-C_{10})$alkynyl, $-(C_3-C_{10})$cycloalkyl, $-(C_8-C_{14})$bicycloalkyl, $-(C_8-C_{14})$tricycloalkyl, $-(C_5-C_{10})$cycloalkenyl,$-(C_8-C_{14})$bicycloalkenyl, $-(C_8-C_{14})$tricycloalkenyl, $-(C_3-C_7)$heterocycle, or $-(C_7-C_{10})$bicycloheterocycle, each of which is unsubstituted or substituted with one or more R^5 groups; or

(c) -phenyl, -naphthyl, $-(C_{14})$aryl, or $-(C_5-C_{10})$heteroaryl, each of which is unsubstituted or substituted with one or more R^7 groups;

each R^3 is independently:

(a) -halo, -CN, -OH, $-NO_2$, or $-NH_2$; or

(b) $-(C_1-C_{10})$alkyl, $-(C_2-C_{10})$alkenyl, $-(C_2-C_{10})$alkynyl, $-(C_3-C_{10})$cycloalkyl, $-(C_8-C_{14})$bicycloalkyl, $-(C_8-C_{14})$tricycloalkyl, $-(C_5-C_{10})$cycloalkenyl,$-(C_8-C_{14})$bicycloalkenyl, $-(C_8-C_{14})$tricycloalkenyl, $-(C_3-C_7)$heterocycle, or $-(C_7-C_{10})$bicycloheterocycle, each of which is unsubstituted or substituted with one or more R^5 groups; or

(c) -phenyl, -naphthyl, $-(C_{14})$aryl or $-(C_5-C_{10})$heteroaryl, each of which is unsubstituted or substituted with one or more R^7 groups;

R^4 is $-(C_1-C_6)$alkyl, or $-O-(C_1-C_6)$alkyl;

each R^5 is independently -CN, -OH, $-(C_1–C_6)$alkyl, $-(C_2–C_6)$alkenyl, $-(C_2–C_6)$alkenyl, -halo, $-N_3$, $-NO_2$, $-N(R^8)_2$, $-CH=NR^8$, $-NR^8OH$, $-OR^8$, $-COR^8$, $-C(O)OR^8$, $-OC(O)R^8$, $-OC(O)OR^8$, $-SR^8$, $-S(O)R^8$, or $-S(O)_2R^8$;

R^6 is -phenyl, -naphthyl, $-(C_3-C_8)$cycloalkyl,$-(C_{14})$aryl, or $-(C_5–C_{10})$heteroaryl, each of which is unsubstituted or substituted with one or more R^7 groups;

each R^7 is independently $-(C_1–C_6)$alkyl, $-(C_2–C_6)$alkenyl, $-(C_2–C_6)$alkynyl, $-(C_3–C_8)$cycloalkyl, $-(C_5–C_8)$cycloalkenyl, -phenyl, $-(C_3–C_5)$heterocycle, $-C(halo)_3$, $-CH_2(halo)$, $-CH(halo)_2$, -CN, -OH, -halo, $-N_3$, $-NO_2$, $-N(R^8)_2$, $-CH=NR^8$, $-NR^8OH$, $-OR^8$, $-COR^8$, $-C(O)OR^8$, $-OC(O)R^8$, $-OC(O)OR^8$, $-SR^8$, $-S(O)R^8$, or $-S(O)_2R^8$;

each R^8 is independently -H, $-(C_1–C_6)$alkyl, $-(C_2–C_6)$alkenyl, $-(C_2–C_6)$alkynyl, $-(C_3–C_8)$cycloalkyl, $-(C_5–C_8)$cycloalkenyl, -phenyl, $-(C_3–C_5)$heterocycle, $-C(halo)_3$,

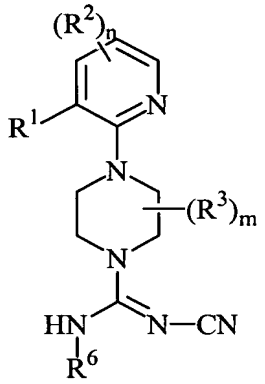
$-CH_2(halo)$, or $-CH(halo)_2$;

each halo is independently -F, -Cl, -Br or -I;

n is an integer ranging from 0 to 3; and

m is an integer ranging from 0 to 2.

The present invention encompasses compounds having the formula (Ia):



(Ia)

and pharmaceutically acceptable salts thereof, wherein:

R^1 is -halo, $-CH_3$, $-NO_2$, -CN, -OH, $-OCH_3$, $-NH_2$, $-C(halo)_3$, $-CH(halo)_2$, or $-CH_2(halo)$;

each R^2 is independently:

(a) -halo, -CN, -OH, $-NO_2$, or $-NH_2$;

(b) $-(C_1-C_{10})$alkyl, $-(C_2-C_{10})$alkenyl, $-(C_2-C_{10})$alkynyl, $-(C_3-C_{10})$cycloalkyl, $-(C_8-C_{14})$bicycloalkyl, $-(C_8-C_{14})$tricycloalkyl, $-(C_5-C_{10})$cycloalkenyl,$-(C_8-C_{14})$bicycloalkenyl, $-(C_8-C_{14})$tricycloalkenyl, $-(C_3-C_7)$heterocycle, or $-(C_7-C_{10})$bicycloheterocycle, each of which is unsubstituted or substituted with one or more R^5 groups; or

(c) -phenyl, -naphthyl, $-(C_{14})$aryl, or $-(C_5-C_{10})$heteroaryl, each of which is unsubstituted or substituted with one or more R^7 groups;

each R^3 is independently:

(a) -halo, -CN, -OH, $-NO_2$, or $-NH_2$; or

(b) $-(C_1-C_{10})$alkyl, $-(C_2-C_{10})$alkenyl, $-(C_2-C_{10})$alkynyl, $-(C_3-C_{10})$cycloalkyl, $-(C_8-C_{14})$bicycloalkyl, $-(C_8-C_{14})$tricycloalkyl, $-(C_5-C_{10})$cycloalkenyl,$-(C_8-C_{14})$bicycloalkenyl, $-(C_8-C_{14})$tricycloalkenyl, $-(C_3-$

C_7)heterocycle, or -(C_7-C_{10})bicycloheterocycle, each of which is unsubstituted or substituted with one or more R^5 groups; or

(c) -phenyl, -naphthyl, -(C_{14})aryl or -(C_5-C_{10})heteroaryl, each of which is unsubstituted or substituted with one or more R^7 groups;

each R^5 is independently -CN, -OH, -(C_1–C_6)alkyl, -(C_2–C_6)alkenyl, -(C_2–C_6)alkenyl, -halo, $-N_3$, $-NO_2$, $-N(R^8)_2$, $-CH=NR^8$, $-NR^8OH$, $-OR^8$, $-COR^8$, $-C(O)OR^8$, $-OC(O)R^8$, $-OC(O)OR^8$, $-SR^8$, $-S(O)R^8$, or $-S(O)_2R^8$;

R^6 is:

(a) -naphthyl, -(C_{14})aryl, or -(C_3-C_8)cycloalkyl each of which is unsubstituted or substituted with one or more R^7 groups; or

(b) pyridyl, furyl, benzofuranyl, thiophenyl, benzothiophenyl, quinolinyl, indolyl, oxazolyl, benzoxazolyl, imidazolyl, benzimidazolyl, thiazolyl, benzothiazolyl, isoxazolyl, pyrazolyl, isothiazolyl, pyridazinyl, pyrimidinyl, pyrazinyl, thiadiazolyl, triazinyl, cinnolinyl, phthalazinyl, or quinazolinyl, each of which is substituted with one or more R^7 groups;

each R^7 is independently -(C_1–C_6)alkyl, -(C_2–C_6)alkenyl, -(C_2–C_6)alkynyl, -(C_3–C_8)cycloalkyl, -(C_5–C_8)cycloalkenyl, -phenyl, -(C_3–C_5)heterocycle, $-C(halo)_3$, $-CH_2(halo)$, $-CH(halo)_2$, -CN, -OH, -halo, $-N_3$, $-NO_2$, $-N(R^8)_2$, $-CH=NR^8$, $-NR^8OH$, $-OR^8$, $-COR^8$, $-C(O)OR^8$, $-OC(O)R^8$, $-OC(O)OR^8$, $-SR^8$, $-S(O)R^8$, or $-S(O)_2R^8$;

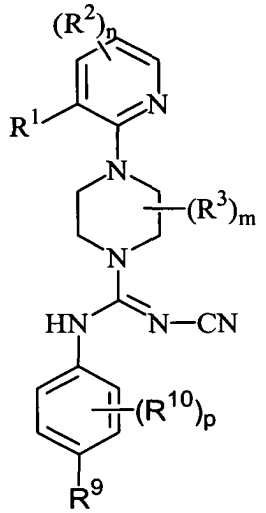
each R^8 is independently -H, -(C_1–C_6)alkyl, -(C_2–C_6)alkenyl, -(C_2–C_6)alkynyl, -(C_3–C_8)cycloalkyl, -(C_5–C_8)cycloalkenyl, -phenyl, -(C_3–C_5)heterocycle, $-C(halo)_3$, $-CH_2(halo)$, or $-CH(halo)_2$;

each halo is independently -F, -Cl, -Br or -I;

n is an integer ranging from 0 to 3; and

m is an integer ranging from 0 to 2.

The present invention encompasses compounds having the formula (Ib):



(Ib)

and pharmaceutically acceptable salts thereof, wherein:

R^1 is -halo, $-CH_3$, $-NO_2$, -CN, -OH, $-OCH_3$, $-NH_2$, $-C(halo)_3$, $-CH(halo)_2$, or $-CH_2(halo)$;

each R^2 is independently:

(a) -halo, -CN, -OH, $-NO_2$, or $-NH_2$;

(b) $-(C_1-C_{10})$alkyl, $-(C_2-C_{10})$alkenyl, $-(C_2-C_{10})$alkynyl, $-(C_3-C_{10})$cycloalkyl, $-(C_8-C_{14})$bicycloalkyl, $-(C_8-C_{14})$tricycloalkyl, $-(C_5-C_{10})$cycloalkenyl,$-(C_8-C_{14})$bicycloalkenyl, $-(C_8-C_{14})$tricycloalkenyl, $-(C_3-C_7)$heterocycle, or $-(C_7-C_{10})$bicycloheterocycle, each of which is unsubstituted or substituted with one or more R^5 groups; or

(c) -phenyl, -naphthyl, $-(C_{14})$aryl, or $-(C_5-C_{10})$heteroaryl, each of which is unsubstituted or substituted with one or more R^7 groups;

each R^3 is independently:

(a) -halo, -CN, -OH, $-NO_2$, or $-NH_2$; or

(b) $-(C_1-C_{10})$alkyl, $-(C_2-C_{10})$alkenyl, $-(C_2-C_{10})$alkynyl, $-(C_3-C_{10})$cycloalkyl, $-(C_8-C_{14})$bicycloalkyl, $-(C_8-C_{14})$tricycloalkyl, $-(C_5-C_{10})$cycloalkenyl,$-(C_8-C_{14})$bicycloalkenyl, $-(C_8-C_{14})$tricycloalkenyl, $-(C_3-C_7)$heterocycle, or $-(C_7-C_{10})$bicycloheterocycle, each of which is unsubstituted or substituted with one or more R^5 groups; or

(c) -phenyl, -naphthyl, -(C_{14})aryl or -(C_5-C_{10})heteroaryl, each of which is unsubstituted or substituted with one or more R^7 groups;

each R^5 is independently -CN, -OH, -(C_1–C_6)alkyl, -(C_2–C_6)alkenyl, -(C_2–C_6)alkenyl, -halo, $-N_3$, $-NO_2$, $-N(R^8)_2$, $-CH=NR^8$, $-NR^8OH$, $-OR^8$, $-COR^8$, $-C(O)OR^8$, $-OC(O)R^8$, $-OC(O)OR^8$, $-SR^8$, $-S(O)R^8$, or $-S(O)_2R^8$;

each R^7, R^9, and R^{10} is independently -(C_1–C_6)alkyl, -(C_2–C_6)alkenyl, -(C_2–C_6)alkynyl, -(C_3–C_8)cycloalkyl, -(C_5–C_8)cycloalkenyl, -phenyl, -(C_3–C_5)heterocycle, $-C(halo)_3$, $-CH(halo)_2$, $-CH_2(halo)$, -CN, -OH, -halo, $-N_3$, $-NO_2$, $-N(R^8)_2$, $-CH=NR^8$, $-NR^8OH$, $-OR^8$, $-COR^8$, $-C(O)OR^8$, $-OC(O)R^8$, $-OC(O)OR^8$, $-SR^8$, $-S(O)R^8$, or $-S(O)_2R^8$;

each R^8 is independently -H, -(C_1–C_6)alkyl, -(C_2–C_6)alkenyl, -(C_2–C_6)alkynyl, -(C_3–C_8)cycloalkyl, -(C_5–C_8)cycloalkenyl, -phenyl, -(C_3–C_5)heterocycle, $-C(halo)_3$, $-CH_2(halo)$, or $-CH(halo)_2$;

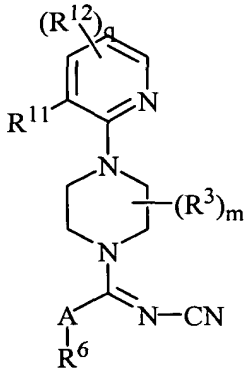
each halo is independently -F, -Cl, -Br or -I;

n is an integer ranging from 0 to 3;

m is an integer ranging from 0 to 2; and

p is an integer ranging from 0 to 4.

The present invention encompasses compounds having the formula (Ic):



(Ic)

and pharmaceutically acceptable salts thereof, wherein:

A is $-NR^4$-, -O-, or -S-;

each R^3 is independently:

(a) -halo, -CN, -OH, $-NO_2$, or $-NH_2$; or

(b) -(C_1-C_{10})alkyl, -(C_2-C_{10})alkenyl, -(C_2-C_{10})alkynyl, -(C_3-C_{10})cycloalkyl, -(C_8-C_{14})bicycloalkyl, -(C_8-C_{14})tricycloalkyl, -(C_5-C_{10})cycloalkenyl,-(C_8-C_{14})bicycloalkenyl, -(C_8-C_{14})tricycloalkenyl, -(C_3-C_7)heterocycle, or -(C_7-C_{10})bicycloheterocycle, each of which is unsubstituted or substituted with one or more R^5 groups; or

(c) -phenyl, -naphthyl, -(C_{14})aryl or -(C_5-C_{10})heteroaryl, each of which is unsubstituted or substituted with one or more R^7 groups;

R^4 is -(C_1-C_6)alkyl, or -O-(C_1-C_6)alkyl;

each R^5 is independently -CN, -OH, -(C_1–C_6)alkyl, -(C_2–C_6)alkenyl, -(C_2–C_6)alkenyl, -halo, $-N_3$, $-NO_2$, $-N(R^8)_2$, $-CH=NR^8$, $-NR^8OH$, $-OR^8$, $-COR^8$, $-C(O)OR^8$, $-OC(O)R^8$, $-OC(O)OR^8$, $-SR^8$, $-S(O)R^8$, or $-S(O)_2R^8$;

R^6 is -phenyl, -naphthyl, -(C_3-C_8)cycloalkyl,-(C_{14})aryl, or -(C_5–C_{10})heteroaryl, each of which is unsubstituted or substituted with one or more R^7 groups;

each R^7 is independently -(C_1–C_6)alkyl, -(C_2–C_6)alkenyl, -(C_2–C_6)alkynyl, -(C_3–C_8)cycloalkyl, -(C_5–C_8)cycloalkenyl, -phenyl, -(C_3–C_5)heterocycle, $-C(halo)_3$, $-CH(halo)_2$, $-CH_2(halo)$, -CN, -OH, -halo, $-N_3$, $-NO_2$, $-N(R^8)_2$, $-CH=NR^8$, $-NR^8OH$, $-OR^8$, $-COR^8$, $-C(O)OR^8$, $-OC(O)R^8$, $-OC(O)OR^8$, $-SR^8$, $-S(O)R^8$, or $-S(O)_2R^8$;

each R^8 is independently -H, -(C_1–C_6)alkyl, -(C_2–C_6)alkenyl, -(C_2–C_6)alkynyl, -(C_3–C_8)cycloalkyl, -(C_5–C_8)cycloalkenyl, -phenyl, -(C_3–C_5)heterocycle, $-C(halo)_3$, $-CH_2(halo)$, or $-CH(halo)_2$;

R^{11} is -hydrogen, -halo, $-CH_3$, $-NO_2$, -CN, -OH, $-OCH_3$, $-NH_2$, $-C(halo)_3$, $-CH(halo)_2$, or $-CH_2(halo)$;

each R^{12} is independently:

(a) -halo, -CN, -OH, $-NO_2$, or $-NH_2$;

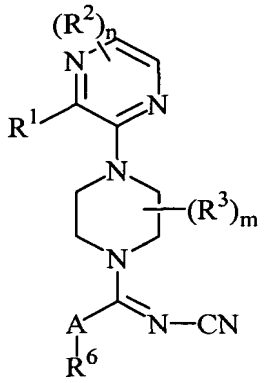
(b) -(C_1-C_{10})alkyl, -(C_2-C_{10})alkenyl, -(C_2-C_{10})alkynyl, -(C_3-C_{10})cycloalkyl, -(C_8-C_{14})bicycloalkyl, -(C_8-C_{14})tricycloalkyl, -(C_5-C_{10})cycloalkenyl,-(C_8-C_{14})bicycloalkenyl, -(C_8-C_{14})tricycloalkenyl, -(C_3-C_7)heterocycle, or -(C_7-C_{10})bicycloheterocycle, each of which is unsubstituted or substituted with one or more R^5 groups; or

(c) -phenyl, -naphthyl, -(C_{14})aryl, or -(C_5-C_{10})heteroaryl, each of which is unsubstituted or substituted with one or more R^7 groups;

m is an integer ranging from 0 to 2; and

q is an integer ranging from 0 to 3.

The present invention also encompasses compounds having the formula (II):



(II)

and pharmaceutically acceptable salts thereof, wherein:

A is $-NR^4-$, -O-, or -S-;

R^1 is -halo, $-CH_3$, $-NO_2$, -CN, -OH, $-OCH_3$, $-NH_2$, $-C(halo)_3$, $-CH(halo)_2$, or $-CH_2(halo)$;

each R^2 is independently:

(a) -halo, -CN, -OH, $-NO_2$, or $-NH_2$;

(b) $-(C_1-C_{10})$alkyl, $-(C_2-C_{10})$alkenyl, $-(C_2-C_{10})$alkynyl, $-(C_3-C_{10})$cycloalkyl, $-(C_8-C_{14})$bicycloalkyl, $-(C_8-C_{14})$tricycloalkyl, $-(C_5-C_{10})$cycloalkenyl,$-(C_8-C_{14})$bicycloalkenyl, $-(C_8-C_{14})$tricycloalkenyl, $-(C_3-C_7)$heterocycle, or $-(C_7-C_{10})$bicycloheterocycle, each of which is unsubstituted or substituted with one or more R^5 groups; or

(c) -phenyl, -naphthyl, $-(C_{14})$aryl, or $-(C_5-C_{10})$heteroaryl, each of which is unsubstituted or substituted with one or more R^7 groups;

each R^3 is independently:

(a) -halo, -CN, -OH, $-NO_2$, or $-NH_2$;

(b) $-(C_1-C_{10})$alkyl, $-(C_2-C_{10})$alkenyl, $-(C_2-C_{10})$alkynyl, $-(C_3-C_{10})$cycloalkyl, $-(C_8-C_{14})$bicycloalkyl, $-(C_8-C_{14})$tricycloalkyl, $-(C_5-C_{10})$cycloalkenyl,$-(C_8-C_{14})$bicycloalkenyl, $-(C_8-C_{14})$tricycloalkenyl, $-(C_3-$

C_7)heterocycle, or -(C_7-C_{10})bicycloheterocycle, each of which is unsubstituted or substituted with one or more R^5 groups; or

(c) -phenyl, -naphthyl, -(C_{14})aryl or -(C_5-C_{10})heteroaryl, each of which is unsubstituted or substituted with one or more R^7 groups;

R^4 is hydrogen, -(C_1-C_6)alkyl, or -O-(C_1-C_6)alkyl;

each R^5 is independently -CN, -OH, -(C_1–C_6)alkyl, -(C_2–C_6)alkenyl, -(C_2–C_6)alkenyl, -halo, -N_3, -NO_2, -$N(R^8)_2$, -CH=NR^8, -NR^8OH, -OR^8, -COR^8, -C(O)OR^8, -OC(O)R^8, -OC(O)OR^8, -SR^8, -S(O)R^8, or -$S(O)_2R^8$;

R^6 is -phenyl, -naphthyl, -(C_3-C_8)cycloalkyl,-(C_{14})aryl, or -(C_5–C_{10})heteroaryl, each of which is unsubstituted or substituted with one or more R^7 groups;

each R^7 is independently -(C_1–C_6)alkyl, -(C_2–C_6)alkenyl, -(C_2–C_6)alkynyl, -(C_3–C_8)cycloalkyl, -(C_5–C_8)cycloalkenyl, -phenyl, -(C_3–C_5)heterocycle, -C(halo)$_3$, -CH_2(halo), -CH(halo)$_2$, -CN, -OH, -halo, -N_3, -NO_2, -$N(R^8)_2$, -CH=NR^8, -NR^8OH, -OR^8, -COR^8, -C(O)OR^8, -OC(O)R^8, -OC(O)OR^8, -SR^8, -S(O)R^8, or -$S(O)_2R^8$;

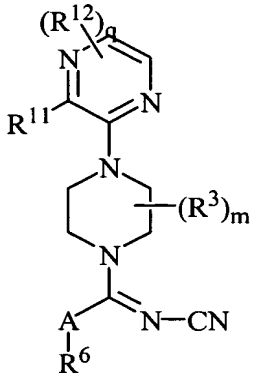
each R^8 is independently -H, -(C_1–C_6)alkyl, -(C_2–C_6)alkenyl, -(C_2–C_6)alkynyl, -(C_3–C_8)cycloalkyl, -(C_5–C_8)cycloalkenyl, -phenyl, -(C_3–C_5)heterocycle, -C(halo)$_3$, -CH_2(halo), or -CH(halo)$_2$;

each halo is independently -F, -Cl, -Br or -I;

n is an integer ranging from 0 to 2; and

m is an integer ranging from 0 to 2.

The present invention also encompasses compounds having the formula (IIa):



(IIa)

and pharmaceutically acceptable salts thereof, wherein:

A is $-NR^4-$, -O-, or -S-;

each R^3 is independently:

(a) -halo, -CN, -OH, $-NO_2$, or $-NH_2$;

(b) $-(C_1-C_{10})$alkyl, $-(C_2-C_{10})$alkenyl, $-(C_2-C_{10})$alkynyl, $-(C_3-C_{10})$cycloalkyl, $-(C_8-C_{14})$bicycloalkyl, $-(C_8-C_{14})$tricycloalkyl, $-(C_5-C_{10})$cycloalkenyl,$-(C_8-C_{14})$bicycloalkenyl, $-(C_8-C_{14})$tricycloalkenyl, $-(C_3-C_7)$heterocycle, or $-(C_7-C_{10})$bicycloheterocycle, each of which is unsubstituted or substituted with one or more R^5 groups; or

(c) -phenyl, -naphthyl, $-(C_{14})$aryl or $-(C_5-C_{10})$heteroaryl, each of which is unsubstituted or substituted with one or more R^7 groups;

R^4 is hydrogen, $-(C_1-C_6)$alkyl, or $-O-(C_1-C_6)$alkyl;

each R^5 is independently -CN, -OH, $-(C_1–C_6)$alkyl, $-(C_2–C_6)$alkenyl, $-(C_2–C_6)$alkenyl, -halo, $-N_3$, $-NO_2$, $-N(R^8)_2$, $-CH=NR^8$, $-NR^8OH$, $-OR^8$, $-COR^8$, $-C(O)OR^8$, $-OC(O)R^8$, $-OC(O)OR^8$, $-SR^8$, $-S(O)R^8$, or $-S(O)_2R^8$;

R^6 is -phenyl, -naphthyl, $-(C_3-C_8)$cycloalkyl,$-(C_{14})$aryl, or $-(C_5–C_{10})$heteroaryl, each of which is unsubstituted or substituted with one or more R^7 groups;

each R^7 is independently $-(C_1–C_6)$alkyl, $-(C_2–C_6)$alkenyl, $-(C_2–C_6)$alkynyl, $-(C_3–C_8)$cycloalkyl, $-(C_5–C_8)$cycloalkenyl, -phenyl, $-(C_3–C_5)$heterocycle, $-C(halo)_3$, $-CH_2(halo)$, $-CH(halo)_2$, -CN, -OH, -halo, $-N_3$, $-NO_2$, $-N(R^8)_2$, $-CH=NR^8$, $-NR^8OH$, $-OR^8$, $-COR^8$, $-C(O)OR^8$, $-OC(O)R^8$, $-OC(O)OR^8$, $-SR^8$, $-S(O)R^8$, or $-S(O)_2R^8$;

each R^8 is independently -H, $-(C_1–C_6)$alkyl, $-(C_2–C_6)$alkenyl, $-(C_2–C_6)$alkynyl, $-(C_3–C_8)$cycloalkyl, $-(C_5–C_8)$cycloalkenyl, -phenyl, $-(C_3–C_5)$heterocycle, $-C(halo)_3$, $-CH_2(halo)$, or $-CH(halo)_2$;

R^{11} is -hydrogen, -halo, $-CH_3$, $-NO_2$, -CN, -OH, $-OCH_3$, $-NH_2$, $-C(halo)_3$, $-CH(halo)_2$, or $-CH_2(halo)$;

each R^{12} is independently:

(a) -halo, -CN, -OH, $-NO_2$, or $-NH_2$;

(b) $-(C_1-C_{10})$alkyl, $-(C_2-C_{10})$alkenyl, $-(C_2-C_{10})$alkynyl, $-(C_3-C_{10})$cycloalkyl, $-(C_8-C_{14})$bicycloalkyl, $-(C_8-C_{14})$tricycloalkyl, $-(C_5-C_{10})$cycloalkenyl,$-(C_8-C_{14})$bicycloalkenyl, $-(C_8-C_{14})$tricycloalkenyl, $-(C_3-$

C_7)heterocycle, or -(C_7-C_{10})bicycloheterocycle, each of which is unsubstituted or substituted with one or more R^5 groups; or

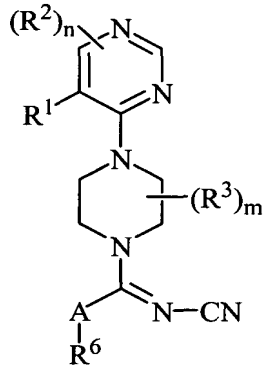
(c) -phenyl, -naphthyl, -(C_{14})aryl, or -(C_5-C_{10})heteroaryl, each of which is unsubstituted or substituted with one or more R^7 groups; and

each halo is independently -F, -Cl, -Br or -I;

q is an integer ranging from 0 to 2; and

m is an integer ranging from 0 to 2.

The present invention also encompasses compounds having the formula (III):



(III)

and pharmaceutically acceptable salts thereof, wherein:

A is -NR^4-, -O-, or -S-;

R^1 is -halo, -CH_3, -NO_2, -CN, -OH, -OCH_3, -NH_2, -C(halo)$_3$, -CH(halo)$_2$, or -CH_2(halo);

each R^2 is independently:

(a) -halo, -CN, -OH, -NO_2, or -NH_2;

(b) -(C_1-C_{10})alkyl, -(C_2-C_{10})alkenyl, -(C_2-C_{10})alkynyl, -(C_3-C_{10})cycloalkyl, -(C_8-C_{14})bicycloalkyl, -(C_8-C_{14})tricycloalkyl, -(C_5-C_{10})cycloalkenyl,-(C_8-C_{14})bicycloalkenyl, -(C_8-C_{14})tricycloalkenyl, -(C_3-C_7)heterocycle, or -(C_7-C_{10})bicycloheterocycle, each of which is unsubstituted or substituted with one or more R^5 groups; or

(c) -phenyl, -naphthyl, -(C_{14})aryl, or -(C_5-C_{10})heteroaryl, each of which is unsubstituted or substituted with one or more R^7 groups;

each R^3 is independently:

(a) -halo, -CN, -OH, $-NO_2$, or $-NH_2$;

(b) $-(C_1-C_{10})$alkyl, $-(C_2-C_{10})$alkenyl, $-(C_2-C_{10})$alkynyl, $-(C_3-C_{10})$cycloalkyl, $-(C_8-C_{14})$bicycloalkyl, $-(C_8-C_{14})$tricycloalkyl, $-(C_5-C_{10})$cycloalkenyl,$-(C_8-C_{14})$bicycloalkenyl, $-(C_8-C_{14})$tricycloalkenyl, $-(C_3-C_7)$heterocycle, or $-(C_7-C_{10})$bicycloheterocycle, each of which is unsubstituted or substituted with one or more R^5 groups; or

(c) -phenyl, -naphthyl, $-(C_{14})$aryl or $-(C_5-C_{10})$heteroaryl, each of which is unsubstituted or substituted with one or more R^7 groups;

R^4 is $-(C_1-C_6)$alkyl, or $-O-(C_1-C_6)$alkyl;

each R^5 is independently -CN, -OH, $-(C_1–C_6)$alkyl, $-(C_2–C_6)$alkenyl, $-(C_2–C_6)$alkenyl, -halo, $-N_3$, $-NO_2$, $-N(R^8)_2$, $-CH=NR^8$, $-NR^8OH$, $-OR^8$, $-COR^8$, $-C(O)OR^8$, $-OC(O)R^8$, $-OC(O)OR^8$, $-SR^8$, $-S(O)R^8$, or $-S(O)_2R^8$;

R^6 is -phenyl, -naphthyl, $-(C_3-C_8)$cycloalkyl,$-(C_{14})$aryl, or $-(C_5–C_{10})$heteroaryl, each of which is unsubstituted or substituted with one or more R^7 groups;

each R^7 is independently $-(C_1–C_6)$alkyl, $-(C_2–C_6)$alkenyl, $-(C_2–C_6)$alkynyl, $-(C_3–C_8)$cycloalkyl, $-(C_5–C_8)$cycloalkenyl, -phenyl, $-(C_3–C_5)$heterocycle, $-C(halo)_3$, $-CH(halo)_2$, $-CH_2(halo)$, -CN, -OH, -halo, $-N_3$, $-NO_2$, $-N(R^8)_2$, $-CH=NR^8$, $-NR^8OH$, $-OR^8$, $-COR^8$, $-C(O)OR^8$, $-OC(O)R^8$, $-OC(O)OR^8$, $-SR^8$, $-S(O)R^8$, or $-S(O)_2R^8$;

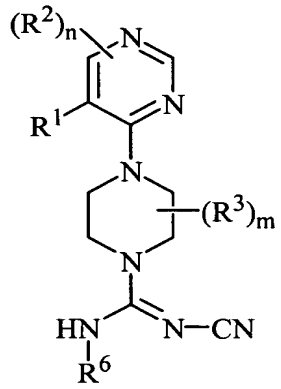
each R^8 is independently -H, $-(C_1–C_6)$alkyl, $-(C_2–C_6)$alkenyl, $-(C_2–C_6)$alkynyl, $-(C_3–C_8)$cycloalkyl, $-(C_5–C_8)$cycloalkenyl, -phenyl, $-(C_3–C_5)$heterocycle, $-C(halo)_3$, $-CH_2(halo)$, or $-CH(halo)_2$;

each halo is independently -F, -Cl, -Br or -I;

n is an integer ranging from 0 to 2; and

m is an integer ranging from 0 to 2.

The present invention encompasses compounds having the formula (IIIa):



(IIIa)

and pharmaceutically acceptable salts thereof, wherein:

R^1 is -halo, $-CH_3$, $-NO_2$, -CN, -OH, $-OCH_3$, $-NH_2$, $-C(halo)_3$, $-CH(halo)_2$, or $-CH_2(halo)$;

each R^2 is independently:

(a) -halo, -CN, -OH, $-NO_2$, or $-NH_2$;

(b) $-(C_1-C_{10})$alkyl, $-(C_2-C_{10})$alkenyl, $-(C_2-C_{10})$alkynyl, $-(C_3-C_{10})$cycloalkyl, $-(C_8-C_{14})$bicycloalkyl, $-(C_8-C_{14})$tricycloalkyl, $-(C_5-C_{10})$cycloalkenyl,$-(C_8-C_{14})$bicycloalkenyl, $-(C_8-C_{14})$tricycloalkenyl, $-(C_3-C_7)$heterocycle, or $-(C_7-C_{10})$bicycloheterocycle, each of which is unsubstituted or substituted with one or more R^5 groups; or

(c) -phenyl, -naphthyl, $-(C_{14})$aryl, or $-(C_5-C_{10})$heteroaryl, each of which is unsubstituted or substituted with one or more R^7 groups;

each R^3 is independently:

(a) -halo, -CN, -OH, $-NO_2$, or $-NH_2$; or

(b) $-(C_1-C_{10})$alkyl, $-(C_2-C_{10})$alkenyl, $-(C_2-C_{10})$alkynyl, $-(C_3-C_{10})$cycloalkyl, $-(C_8-C_{14})$bicycloalkyl, $-(C_8-C_{14})$tricycloalkyl, $-(C_5-C_{10})$cycloalkenyl,$-(C_8-C_{14})$bicycloalkenyl, $-(C_8-C_{14})$tricycloalkenyl, $-(C_3-C_7)$heterocycle, or $-(C_7-C_{10})$bicycloheterocycle, each of which is unsubstituted or substituted with one or more R^5 groups; or

(c) -phenyl, -naphthyl, $-(C_{14})$aryl or $-(C_5-C_{10})$heteroaryl, each of which is unsubstituted or substituted with one or more R^7 groups;

each R^5 is independently -CN, -OH, -$(C_1$–$C_6)$alkyl, -$(C_2$–$C_6)$alkenyl, -$(C_2$–$C_6)$alkenyl, -halo, -N_3, -NO_2, -$N(R^8)_2$, -CH=NR^8, -NR^8OH, -OR^8, -COR^8, -C(O)OR^8, -OC(O)R^8, -OC(O)OR^8, -SR^8, -S(O)R^8, or -$S(O)_2R^8$;

R^6 is:

(a), -naphthyl, -(C_{14})aryl, or -$(C_3$-$C_8)$cycloalkyl each of which is unsubstituted or substituted with one or more R^7 groups; or

(b) pyridyl, furyl, benzofuranyl, thiophenyl, benzothiophenyl, quinolinyl, indolyl, oxazolyl, benzoxazolyl, imidazolyl, benzimidazolyl, thiazolyl, benzothiazolyl, isoxazolyl, pyrazolyl, isothiazolyl, pyridazinyl, pyrimidinyl, pyrazinyl, thiadiazolyl, triazinyl, cinnolinyl, phthalazinyl, or quinazolinyl, each of which is substituted with one or more R^7 groups;

each R^7 is independently -$(C_1$–$C_6)$alkyl, -$(C_2$–$C_6)$alkenyl, -$(C_2$–$C_6)$alkynyl, -$(C_3$–$C_8)$cycloalkyl, -$(C_5$–$C_8)$cycloalkenyl, -phenyl, -$(C_3$–$C_5)$heterocycle, -C(halo)$_3$, -CH(halo)$_2$, -CH_2(halo), -CN, -OH, -halo, -N_3, -NO_2, -$N(R^8)_2$, -CH=NR^8, -NR^8OH, -OR^8, -COR^8, -C(O)OR^8, -OC(O)R^8, -OC(O)OR^8, -SR^8, -S(O)R^8, or -$S(O)_2R^8$;

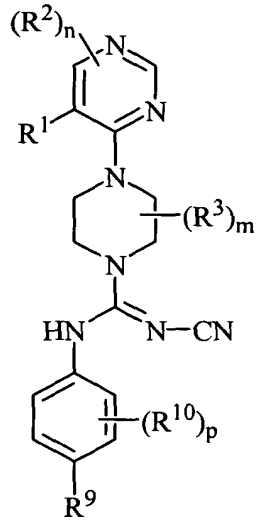
each R^8 is independently -H, -$(C_1$–$C_6)$alkyl, -$(C_2$–$C_6)$alkenyl, -$(C_2$–$C_6)$alkynyl, -$(C_3$–$C_8)$cycloalkyl, -$(C_5$–$C_8)$cycloalkenyl, -phenyl, -$(C_3$–$C_5)$heterocycle, -C(halo)$_3$, -CH_2(halo), or -CH(halo)$_2$;

each halo is independently -F, -Cl, -Br or -I;

n is an integer ranging from 0 to 2; and

m is an integer ranging from 0 to 2.

The present invention encompasses compounds having the formula (IIIb):



(IIIb)

and pharmaceutically acceptable salts thereof, wherein:

R^1 is -halo, $-CH_3$, $-NO_2$, -CN, -OH, $-OCH_3$, $-NH_2$, $-C(halo)_3$, $-CH(halo)_2$, or $-CH_2(halo)$;

each R^2 is independently:

(a) -halo, -CN, -OH, $-NO_2$, or $-NH_2$;

(b) $-(C_1-C_{10})$alkyl, $-(C_2-C_{10})$alkenyl, $-(C_2-C_{10})$alkynyl, $-(C_3-C_{10})$cycloalkyl, $-(C_8-C_{14})$bicycloalkyl, $-(C_8-C_{14})$tricycloalkyl, $-(C_5-C_{10})$cycloalkenyl,$-(C_8-C_{14})$bicycloalkenyl, $-(C_8-C_{14})$tricycloalkenyl, $-(C_3-C_7)$heterocycle, or $-(C_7-C_{10})$bicycloheterocycle, each of which is unsubstituted or substituted with one or more R^5 groups; or

(c) -phenyl, -naphthyl, $-(C_{14})$aryl, or $-(C_5-C_{10})$heteroaryl, each of which is unsubstituted or substituted with one or more R^7 groups;

each R^3 is independently:

(a) -halo, -CN, -OH, $-NO_2$, or $-NH_2$; or

(b) $-(C_1-C_{10})$alkyl, $-(C_2-C_{10})$alkenyl, $-(C_2-C_{10})$alkynyl, $-(C_3-C_{10})$cycloalkyl, $-(C_8-C_{14})$bicycloalkyl, $-(C_8-C_{14})$tricycloalkyl, $-(C_5-C_{10})$cycloalkenyl,$-(C_8-C_{14})$bicycloalkenyl, $-(C_8-C_{14})$tricycloalkenyl, $-(C_3-C_7)$heterocycle, or $-(C_7-C_{10})$bicycloheterocycle, each of which is unsubstituted or substituted with one or more R^5 groups; or

(c) -phenyl, -naphthyl, -(C_{14})aryl or -(C_5-C_{10})heteroaryl, each of which is unsubstituted or substituted with one or more R^7 groups;

each R^5 is independently -CN, -OH, -(C_1–C_6)alkyl, -(C_2–C_6)alkenyl, -(C_2–C_6)alkenyl, -halo, -N_3, -NO_2, -$N(R^8)_2$, -CH=NR^8, -NR^8OH, -OR^8, -COR^8, -C(O)OR^8, -OC(O)R^8, -OC(O)OR^8, -SR^8, -S(O)R^8, or -$S(O)_2R^8$;

each R^7, R^9, and R^{10} is independently -(C_1–C_6)alkyl, -(C_2–C_6)alkenyl, -(C_2–C_6)alkynyl, -(C_3–C_8)cycloalkyl, -(C_5–C_8)cycloalkenyl, -phenyl, -(C_3–C_5)heterocycle, -C(halo)$_3$, -CH(halo)$_2$, -CH_2(halo), -CN, -OH, -halo, -N_3, -NO_2, -$N(R^8)_2$, -CH=NR^8, -NR^8OH, -OR^8, -COR^8, -C(O)OR^8, -OC(O)R^8, -OC(O)OR^8, -SR^8, -S(O)R^8, or -$S(O)_2R^8$;

each R^8 is independently -H, -(C_1–C_6)alkyl, -(C_2–C_6)alkenyl, -(C_2–C_6)alkynyl, -(C_3–C_8)cycloalkyl, -(C_5–C_8)cycloalkenyl, -phenyl, -(C_3–C_5)heterocycle, -C(halo)$_3$, -CH_2(halo), or -CH(halo)$_2$;

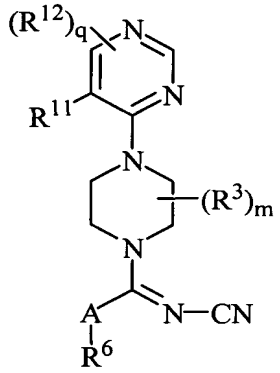
each halo is independently -F, -Cl, -Br or -I;

n is an integer ranging from 0 to 2;

m is an integer ranging from 0 to 2; and

p is an integer ranging from 0 to 4.

The present invention also encompasses compounds having the formula (IIIc):



(IIIc)

and pharmaceutically acceptable salts thereof, wherein:

A is -NR^4-, -O-, or -S-;

each R^3 is independently:

(a) -halo, -CN, -OH, -NO_2, or -NH_2;

(b) -(C_1-C_{10})alkyl, -(C_2-C_{10})alkenyl, -(C_2-C_{10})alkynyl, -(C_3-C_{10})cycloalkyl, -(C_8-C_{14})bicycloalkyl, -(C_8-C_{14})tricycloalkyl, -(C_5-C_{10})cycloalkenyl,-(C_8-C_{14})bicycloalkenyl, -(C_8-C_{14})tricycloalkenyl, -(C_3-C_7)heterocycle, or -(C_7-C_{10})bicycloheterocycle, each of which is unsubstituted or substituted with one or more R^5 groups; or

(c) -phenyl, -naphthyl, -(C_{14})aryl or -(C_5-C_{10})heteroaryl, each of which is unsubstituted or substituted with one or more R^7 groups;

R^4 is -(C_1-C_6)alkyl, or -O-(C_1-C_6)alkyl;

each R^5 is independently -CN, -OH, -(C_1–C_6)alkyl, -(C_2–C_6)alkenyl, -(C_2–C_6)alkenyl, -halo, $-N_3$, $-NO_2$, $-N(R^8)_2$, $-CH{=}NR^8$, $-NR^8OH$, $-OR^8$, $-COR^8$, $-C(O)OR^8$, $-OC(O)R^8$, $-OC(O)OR^8$, $-SR^8$, $-S(O)R^8$, or $-S(O)_2R^8$;

R^6 is -phenyl, -naphthyl, -(C_3-C_8)cycloalkyl,-(C_{14})aryl, or -(C_5–C_{10})heteroaryl, each of which is unsubstituted or substituted with one or more R^7 groups;

each R^7 is independently -(C_1–C_6)alkyl, -(C_2–C_6)alkenyl, -(C_2–C_6)alkynyl, -(C_3–C_8)cycloalkyl, -(C_5–C_8)cycloalkenyl, -phenyl, -(C_3–C_5)heterocycle, $-C(halo)_3$, $-CH(halo)_2$, $-CH_2(halo)$, -CN, -OH, -halo, $-N_3$, $-NO_2$, $-N(R^8)_2$, $-CH{=}NR^8$, $-NR^8OH$, $-OR^8$, $-COR^8$, $-C(O)OR^8$, $-OC(O)R^8$, $-OC(O)OR^8$, $-SR^8$, $-S(O)R^8$, or $-S(O)_2R^8$;

each R^8 is independently -H, -(C_1–C_6)alkyl, -(C_2–C_6)alkenyl, -(C_2–C_6)alkynyl, -(C_3–C_8)cycloalkyl, -(C_5–C_8)cycloalkenyl, -phenyl, -(C_3–C_5)heterocycle, $-C(halo)_3$, $-CH_2(halo)$, or $-CH(halo)_2$;

R^{11} is -hydrogen, -halo, $-CH_3$, $-NO_2$, -CN, -OH, $-OCH_3$, $-NH_2$, $-C(halo)_3$, $-CH(halo)_2$, or $-CH_2(halo)$;

each R^{12} is independently:

(a) -halo, -CN, -OH, $-NO_2$, or $-NH_2$;

(b) -(C_1-C_{10})alkyl, -(C_2-C_{10})alkenyl, -(C_2-C_{10})alkynyl, -(C_3-C_{10})cycloalkyl, -(C_8-C_{14})bicycloalkyl, -(C_8-C_{14})tricycloalkyl, -(C_5-C_{10})cycloalkenyl,-(C_8-C_{14})bicycloalkenyl, -(C_8-C_{14})tricycloalkenyl, -(C_3-C_7)heterocycle, or -(C_7-C_{10})bicycloheterocycle, each of which is unsubstituted or substituted with one or more R^5 groups; or

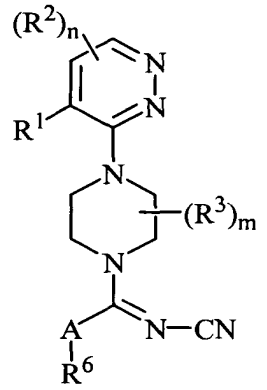
(c) -phenyl, -naphthyl, -(C_{14})aryl, or -(C_5-C_{10})heteroaryl, each of which is unsubstituted or substituted with one or more R^7 groups;

each halo is independently -F, -Cl, -Br or -I;

q is an integer ranging from 0 to 2; and

m is an integer ranging from 0 to 2.

The present invention also encompasses compounds having the formula (IV):



(IV)

and pharmaceutically acceptable salts thereof, wherein:

A is $-NR^4-$, -O-, or -S-;

R^1 is -halo, $-CH_3$, $-NO_2$, -CN, -OH, $-OCH_3$, $-NH_2$, $-C(halo)_3$, $-CH(halo)_2$, or $-CH_2(halo)$;

each R^2 is independently:

(a) -halo, -CN, -OH, $-NO_2$, or $-NH_2$;

(b) $-(C_1-C_{10})$alkyl, $-(C_2-C_{10})$alkenyl, $-(C_2-C_{10})$alkynyl, $-(C_3-C_{10})$cycloalkyl, $-(C_8-C_{14})$bicycloalkyl, $-(C_8-C_{14})$tricycloalkyl, $-(C_5-C_{10})$cycloalkenyl,$-(C_8-C_{14})$bicycloalkenyl, $-(C_8-C_{14})$tricycloalkenyl, $-(C_3-C_7)$heterocycle, or $-(C_7-C_{10})$bicycloheterocycle, each of which is unsubstituted or substituted with one or more R^5 groups; or

(c) -phenyl, -naphthyl, $-(C_{14})$aryl, or $-(C_5-C_{10})$heteroaryl, each of which is unsubstituted or substituted with one or more R^7 groups;

each R^3 is independently:

(a) -halo, -CN, -OH, $-NO_2$, or $-NH_2$;

(b) $-(C_1-C_{10})$alkyl, $-(C_2-C_{10})$alkenyl, $-(C_2-C_{10})$alkynyl, $-(C_3-C_{10})$cycloalkyl, $-(C_8-C_{14})$bicycloalkyl, $-(C_8-C_{14})$tricycloalkyl, $-(C_5-$

C_{10})cycloalkenyl,-(C_8-C_{14})bicycloalkenyl, -(C_8-C_{14})tricycloalkenyl, -(C_3-C_7)heterocycle, or -(C_7-C_{10})bicycloheterocycle, each of which is unsubstituted or substituted with one or more R^5 groups; or

(c) -phenyl, -naphthyl, -(C_{14})aryl or -(C_5-C_{10})heteroaryl, each of which is unsubstituted or substituted with one or more R^7 groups;

R^4 is hydrogen, -(C_1-C_6)alkyl, or -O-(C_1-C_6)alkyl;

each R^5 is independently -CN, -OH, -(C_1–C_6)alkyl, -(C_2–C_6)alkenyl, -(C_2–C_6)alkenyl, -halo, $-N_3$, $-NO_2$, $-N(R^8)_2$, $-CH=NR^8$, $-NR^8OH$, $-OR^8$, $-COR^8$, $-C(O)OR^8$, $-OC(O)R^8$, $-OC(O)OR^8$, $-SR^8$, $-S(O)R^8$, or $-S(O)_2R^8$;

R^6 is -phenyl, -naphthyl, -(C_3-C_8)cycloalkyl,-(C_{14})aryl, or -(C_5–C_{10})heteroaryl, each of which is unsubstituted or substituted with one or more R^7 groups;

each R^7 is independently -(C_1–C_6)alkyl, -(C_2–C_6)alkenyl, -(C_2–C_6)alkynyl, -(C_3–C_8)cycloalkyl, -(C_5–C_8)cycloalkenyl, -phenyl, -(C_3–C_5)heterocycle, $-C(halo)_3$, $-CH(halo)_2$, $-CH_2(halo)$, -CN, -OH, -halo, $-N_3$, $-NO_2$, $-N(R^8)_2$, $-CH=NR^8$, $-NR^8OH$, $-OR^8$, $-COR^8$, $-C(O)OR^8$, $-OC(O)R^8$, $-OC(O)OR^8$, $-SR^8$, $-S(O)R^8$, or $-S(O)_2R^8$;

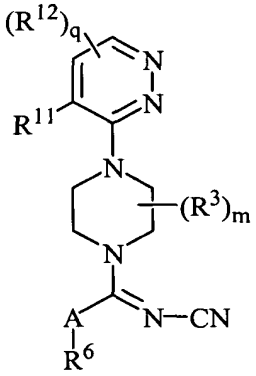
each R^8 is independently -H, -(C_1–C_6)alkyl, -(C_2–C_6)alkenyl, -(C_2–C_6)alkynyl, -(C_3–C_8)cycloalkyl, -(C_5–C_8)cycloalkenyl, -phenyl, -(C_3–C_5)heterocycle, $-C(halo)_3$, $-CH_2(halo)$, or $-CH(halo)_2$;

each halo is independently -F, -Cl, -Br or -I;

n is an integer ranging from 0 to 2; and

m is an integer ranging from 0 to 2.

The present invention also encompasses compounds having the formula (IVa):



(IVa)

and pharmaceutically acceptable salts thereof, wherein:

A is $-NR^4-$, -O-, or -S-;

each R^3 is independently:

(a) -halo, -CN, -OH, $-NO_2$, or $-NH_2$;

(b) $-(C_1-C_{10})$alkyl, $-(C_2-C_{10})$alkenyl, $-(C_2-C_{10})$alkynyl, $-(C_3-C_{10})$cycloalkyl, $-(C_8-C_{14})$bicycloalkyl, $-(C_8-C_{14})$tricycloalkyl, $-(C_5-C_{10})$cycloalkenyl,$-(C_8-C_{14})$bicycloalkenyl, $-(C_8-C_{14})$tricycloalkenyl, $-(C_3-C_7)$heterocycle, or $-(C_7-C_{10})$bicycloheterocycle, each of which is unsubstituted or substituted with one or more R^5 groups; or

(c) -phenyl, -naphthyl, $-(C_{14})$aryl or $-(C_5-C_{10})$heteroaryl, each of which is unsubstituted or substituted with one or more R^7 groups;

R^4 is hydrogen, $-(C_1-C_6)$alkyl, or $-O-(C_1-C_6)$alkyl;

each R^5 is independently -CN, -OH, $-(C_1–C_6)$alkyl, $-(C_2–C_6)$alkenyl, $-(C_2–C_6)$alkenyl, -halo, $-N_3$, $-NO_2$, $-N(R^8)_2$, $-CH=NR^8$, $-NR^8OH$, $-OR^8$, $-COR^8$, $-C(O)OR^8$, $-OC(O)R^8$, $-OC(O)OR^8$, $-SR^8$, $-S(O)R^8$, or $-S(O)_2R^8$;

R^6 is -phenyl, -naphthyl, $-(C_3-C_8)$cycloalkyl,$-(C_{14})$aryl, or $-(C_5–C_{10})$heteroaryl, each of which is unsubstituted or substituted with one or more R^7 groups;

each R^7 is independently $-(C_1–C_6)$alkyl, $-(C_2–C_6)$alkenyl, $-(C_2–C_6)$alkynyl, $-(C_3–C_8)$cycloalkyl, $-(C_5–C_8)$cycloalkenyl, -phenyl, $-(C_3–C_5)$heterocycle, $-C(halo)_3$, $-CH(halo)_2$, $-CH_2(halo)$, -CN, -OH, -halo, $-N_3$, $-NO_2$, $-N(R^8)_2$, $-CH=NR^8$, $-NR^8OH$, $-OR^8$, $-COR^8$, $-C(O)OR^8$, $-OC(O)R^8$, $-OC(O)OR^8$, $-SR^8$, $-S(O)R^8$, or $-S(O)_2R^8$;

each R^8 is independently -H, $-(C_1–C_6)$alkyl, $-(C_2–C_6)$alkenyl, $-(C_2–C_6)$alkynyl, $-(C_3–C_8)$cycloalkyl, $-(C_5–C_8)$cycloalkenyl, -phenyl, $-(C_3–C_5)$heterocycle, $-C(halo)_3$, $-CH_2(halo)$, or $-CH(halo)_2$;

R^{11} is -hydrogen, -halo, $-CH_3$, $-NO_2$, -CN, -OH, $-OCH_3$, $-NH_2$, $-C(halo)_3$, $-CH(halo)_2$, or $-CH_2(halo)$;

each R^{12} is independently:

(a) -halo, -CN, -OH, $-NO_2$, or $-NH_2$;

(b) $-(C_1-C_{10})$alkyl, $-(C_2-C_{10})$alkenyl, $-(C_2-C_{10})$alkynyl, $-(C_3-C_{10})$cycloalkyl, $-(C_8-C_{14})$bicycloalkyl, $-(C_8-C_{14})$tricycloalkyl, $-(C_5-C_{10})$cycloalkenyl,$-(C_8-C_{14})$bicycloalkenyl, $-(C_8-C_{14})$tricycloalkenyl, $-(C_3-$

C_7)heterocycle, or -(C_7-C_{10})bicycloheterocycle, each of which is unsubstituted or substituted with one or more R^5 groups; or

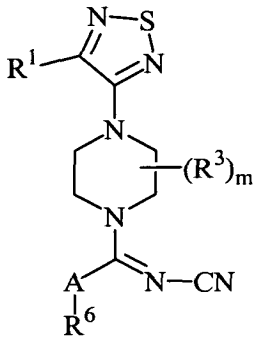
(c) -phenyl, -naphthyl, -(C_{14})aryl, or -(C_5-C_{10})heteroaryl, each of which is unsubstituted or substituted with one or more R^7 groups;

each halo is independently -F, -Cl, -Br or -I;

q is an integer ranging from 0 to 2; and

m is an integer ranging from 0 to 2.

The present invention also encompasses compounds having the formula (V):



(V)

and pharmaceutically acceptable salts thereof, wherein:

A is -NR^4-, -O-, or -S-;

R^1 is -hydrogen, -halo, -CH_3, -NO_2, -CN, -OH, -OCH_3, -NH_2, -C(halo)$_3$, -CH(halo)$_2$, or -CH_2(halo);

each R^3 is independently:

(a) -halo, -CN, -OH, -NO_2, or -NH_2;

(b) -(C_1-C_{10})alkyl, -(C_2-C_{10})alkenyl, -(C_2-C_{10})alkynyl, -(C_3-C_{10})cycloalkyl, -(C_8-C_{14})bicycloalkyl, -(C_8-C_{14})tricycloalkyl, -(C_5-C_{10})cycloalkenyl,-(C_8-C_{14})bicycloalkenyl, -(C_8-C_{14})tricycloalkenyl, -(C_3-C_7)heterocycle, or -(C_7-C_{10})bicycloheterocycle, each of which is unsubstituted or substituted with one or more R^5 groups; or

(c) -phenyl, -naphthyl, -(C_{14})aryl or -(C_5-C_{10})heteroaryl, each of which is unsubstituted or substituted with one or more R^7 groups;

R^4 is hydrogen, -(C_1-C_6)alkyl, or -O-(C_1-C_6)alkyl;

each R^5 is independently -CN, -OH, -$(C_1$–$C_6)$alkyl, -$(C_2$–$C_6)$alkenyl, -$(C_2$–$C_6)$alkenyl, -halo, -N_3, -NO_2, -$N(R^8)_2$, -$CH{=}NR^8$, -NR^8OH, -OR^8, -COR^8, -$C(O)OR^8$, -$OC(O)R^8$, -$OC(O)OR^8$, -SR^8, -$S(O)R^8$, or -$S(O)_2R^8$;

R^6 is -phenyl, -naphthyl, -$(C_3$-$C_8)$cycloalkyl,-(C_{14})aryl, or -$(C_5$–$C_{10})$heteroaryl, each of which is unsubstituted or substituted with one or more R^7 groups;

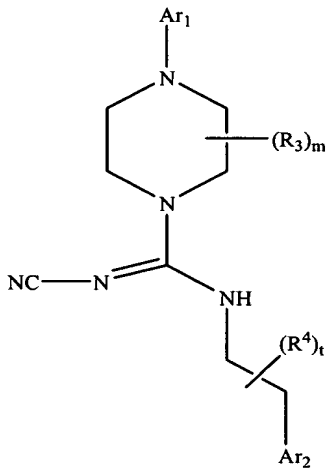
each R^7 is independently -$(C_1$–$C_6)$alkyl, -$(C_2$–$C_6)$alkenyl, -$(C_2$–$C_6)$alkynyl, -$(C_3$–$C_8)$cycloalkyl, -$(C_5$–$C_8)$cycloalkenyl, -phenyl, -$(C_3$–$C_5)$heterocycle, -$C(halo)_3$, -$CH_2(halo)$, -$CH(halo)_2$, -CN, -OH, -halo, -N_3, -NO_2, -$N(R^8)_2$, -$CH{=}NR^8$, -NR^8OH, -OR^8, -COR^8, -$C(O)OR^8$, -$OC(O)R^8$, -$OC(O)OR^8$, -SR^8, -$S(O)R^8$, or -$S(O)_2R^8$;

each R^8 is independently -H, -$(C_1$–$C_6)$alkyl, -$(C_2$–$C_6)$alkenyl, -$(C_2$–$C_6)$alkynyl, -$(C_3$–$C_8)$cycloalkyl, -$(C_5$–$C_8)$cycloalkenyl, -phenyl, -$(C_3$–$C_5)$heterocycle, -$C(halo)_3$, -$CH_2(halo)$, or -$CH(halo)_2$;

each halo is independently -F, -Cl, -Br or -I; and

m is an integer ranging from 0 to 2.

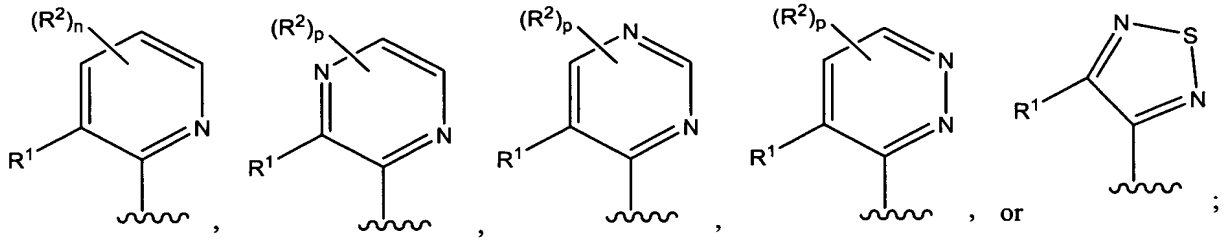
The present invention encompasses compounds having the formula (VI):



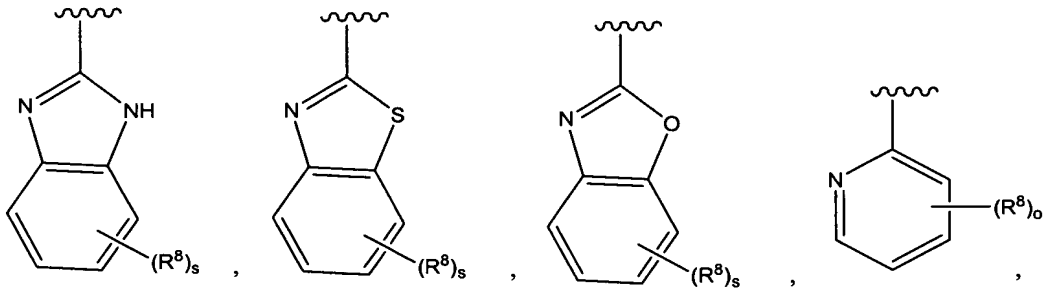
(VI)

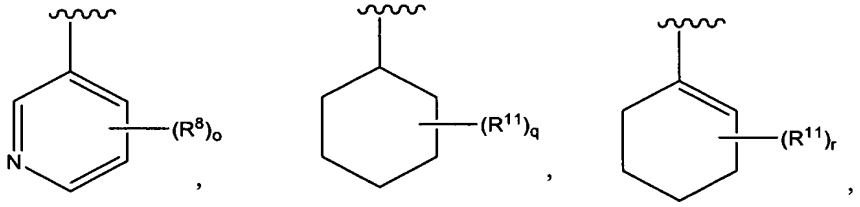
and pharmaceutically acceptable salts thereof, wherein:

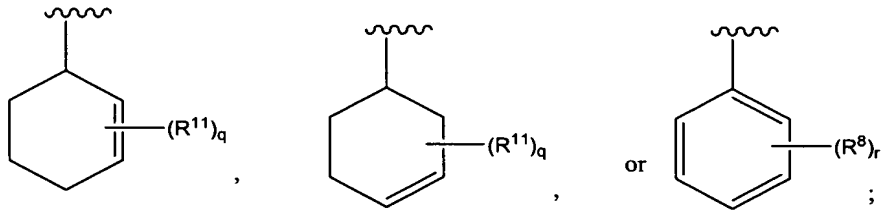
Ar_1 is


(R2)n
R1
N
(R2)p
N
R1
N
(R2)p
R1
N
(R2)p
N
N
R1
N
S
N
R1
N
or

Ar_2 is


N
NH
(R8)s
N
S
(R8)s
N
O
(R8)s
N
(R8)o


N
(R8)o
(R11)q
(R11)r


(R11)q
(R11)q
or
(R8)r

R^1 is -H, -halo, $-CH_3$, $-NO_2$, -CN, -OH, $-OCH_3$, $-NH_2$, $C(halo)_3$, $-CH(halo)_2$, or $-CH_2(halo)$;

each R^2 is independently:

(a) -halo, -CN, -OH, $-NO_2$, or $-NH_2$;

(b) $-(C_1-C_{10})$alkyl, $-(C_2-C_{10})$alkenyl, $-(C_2-C_{10})$alkynyl, $-(C_3-C_{10})$cycloalkyl, $-(C_8-C_{14})$bicycloalkyl, $-(C_8-C_{14})$tricycloalkyl, $-(C_5-C_{10})$cycloalkenyl, $-(C_8-C_{14})$bicycloalkenyl, $-(C_8-C_{14})$tricycloalkenyl, -(3- to 7-membered)heterocycle, or -(7- to 10-membered)bicycloheterocycle, each of which is unsubstituted or substituted with one or more R^5 groups; or

(c) -phenyl, -naphthyl, $-(C_{14})$aryl or -(5- to 10-membered)heteroaryl, each of which is unsubstitute or substituted with one or more R_6 groups;

each R^3 is independently:

(a) -halo, -CN, -OH, $-NO_2$, or $-NH_2$;

(b) $-(C_1-C_{10})$alkyl, $-(C_2-C_{10})$alkenyl, $-(C_2-C_{10})$alkynyl, $-(C_3-C_{10})$cycloalkyl, $-(C_8-C_{14})$bicycloalkyl, $-(C_8-C_{14})$tricycloalkyl, $-(C_5-C_{10})$cycloalkenyl, $-(C_8-C_{14})$bicycloalkenyl, $-(C_8-C_{14})$tricycloalkenyl, -(3- to 7-membered)heterocycle, or -(7- to 10-membered)bicycloheterocycle, each of which is unsubstituted or substituted with one or more R^5 groups; or

(c) -phenyl, -naphthyl, $-(C_{14})$aryl or -(5- to 10-membered) heteroaryl, each of which is unsubstituted or substituted with one or more R^6 groups;

each R^4 is independently $-(C_1-C_6)$alkyl, $-(C_2-C_6)$alkenyl, $-(C_2-C_6)$alkynyl, $-(C_3-C_8)$cycloalkyl, $-(C_5-C_8)$cycloalkenyl, -phenyl, -(3- to 5-membered)heterocycle, $-C(halo)_3$, $-CH(halo)_2$, or $CH_2(halo)$;

each R^5 is independently -CN, -OH, $-(C_1-C_6)$alkyl, $-(C_2-C_6)$alkenyl, $-(C_2-C_6)$alkenyl, -halo, $-N_3$, $-NO_2$, $-N(R^8)_2$, $-CH=NR^8$, $-NR^8OH$, $-OR^8$, $-COR^8$, $-C(O)OR^8$, $-OC(O)R^8$, $-OC(O)OR^8$, $-SR^8$, $-S(O)R^8$, or $-S(O)_2R^8$;

each R^6 is independently $-(C_1-C_6)$alkyl, $-(C_2-C_6)$alkenyl, $-(C_2-C_6)$alkynyl, $-(C_3-C_8)$cycloalkyl, $-(C_5-C_8)$cycloalkenyl, -phenyl, -(3- to 5-membered)heterocycle, $-C(halo)_3$, $-CH(halo)_2$, $-CH_2(halo)$, -CN, -OH, -halo, $-N_3$, $-NO_2$, $-CH=NR_7$, $-NR_7OH$, $-OR_7$, $-COR_7$, $-C(O)OR_7$, $-OC(O)R_7$, $-OC(O)OR_7$, $-SR_7$, $-S(O)R_7$, or $-S(O)_2R_7$;

each R^7 is independently -H, -(C_1–C_6)alkyl, -(C_2–C_6)alkenyl, -(C_2–C_6)alkynyl, -(C_3–C_8)cycloalkyl, -(C_5–C_8)cycloalkenyl, -phenyl, -(3- to 5-membered)heterocycle, -C(halo)$_3$, -CH(halo)$_2$, or CH_2(halo);

each R^8 is independently -(C_1–C_6)alkyl, -(C_2–C_6)alkenyl, -(C_2–C_6)alkynyl, -(C_3-C_8)cycloalkyl, -(C_5–C_8)cycloalkenyl, -phenyl, -C(halo)$_3$, -CH(halo)$_2$, -CH_2(halo), -CN, -OH, -halo, -N_3, -NO_2, -CH=NR_7, -NR_7OH, -OR_7, -COR_7, -C(O)OR_7, -OC(O)R_7, -OC(O)OR_7, -SR_7, -S(O)R_7, or -$S(O)_2R_7$;

each R^{11} is independently -CN, -OH, -(C_1–C_6)alkyl, -(C_2–C_6)alkenyl, -halo, -N_3, -NO_2, -$N(R_7)_2$, -CH=NR_7, -NR_7OH, -OR_7, -COR_7, -C(O)OR_7, -OC(O)R_7, -OC(O)OR_7, -SR_7, -S(O)R_7, or -$S(O)_2R_7$;

each halo is independently -F, -Cl, -Br, or -I;

m is 0 or 1;

n is an integer ranging from 0 to 3;

o is an integer ranging from 0 to 4;

p is an integer ranging from 0 to 2;

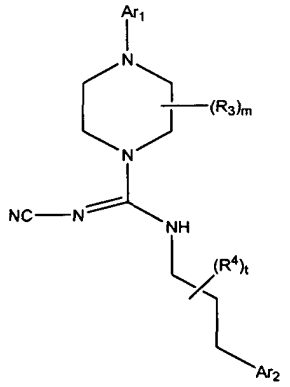
q is an integer ranging from 0 to 6;

r is an integer ranging from 0 to 5;

s is an integer ranging from 0 to 4; and

t is an integer ranging from 0 to 2.

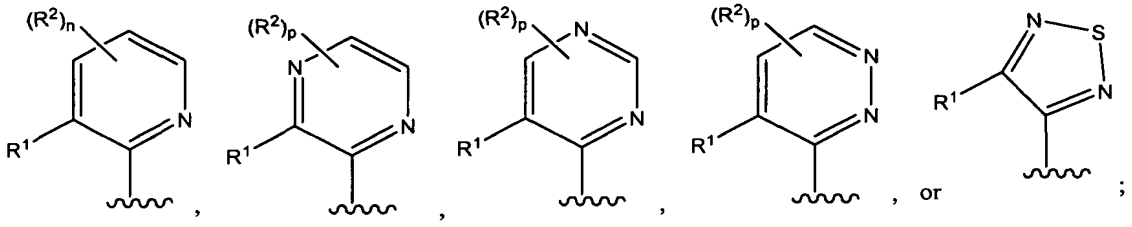
The present invention encompasses compounds having the formula (VII):



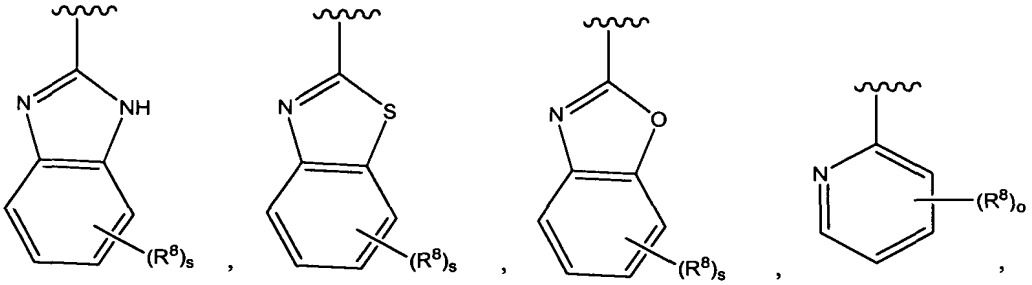
(VII)

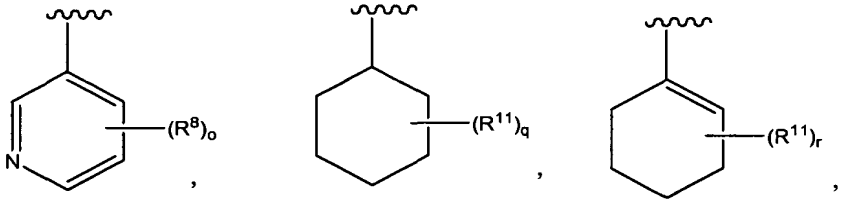
and pharmaceutically acceptable salts thereof, wherein:

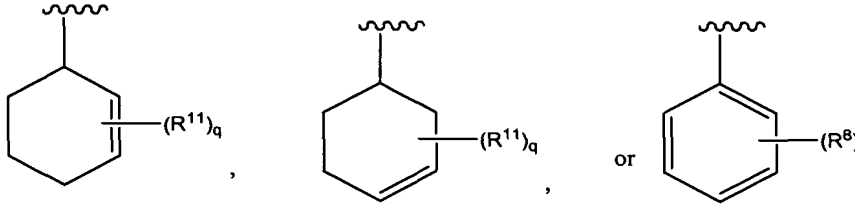
Ar_1 is



Ar_2 is







R^1 is -H, -halo, $-CH_3$, $-NO_2$, -CN, -OH, $-OCH_3$, $-NH_2$, $C(halo)_3$, $-CH(halo)_2$, or $-CH_2(halo)$;

each R^2 is independently:

(a) -halo, -CN, -OH, $-NO_2$, or $-NH_2$;

(b) $-(C_1-C_{10})$alkyl, $-(C_2-C_{10})$alkenyl, $-(C_2-C_{10})$alkynyl, $-(C_3-C_{10})$cycloalkyl, $-(C_8-C_{14})$bicycloalkyl, $-(C_8-C_{14})$tricycloalkyl, $-(C_5-C_{10})$cycloalkenyl, $-(C_8-$

C_{14})bicycloalkenyl, -(C_8-C_{14})tricycloalkenyl, -(3- to 7-membered)heterocycle, or -(7- to 10-membered)bicycloheterocycle, each of which is unsubstituted or substituted with one or more R^5 groups; or

(c) -phenyl, -naphthyl, -(C_{14})aryl or -(5- to 10-membered)heteroaryl, each of which is unsubstitute or substituted with one or more R_6 groups;

each R^3 is independently:

(a) -halo, -CN, -OH, -NO_2, or -NH_2;

(b) -(C_1-C_{10})alkyl, -(C_2-C_{10})alkenyl, -(C_2-C_{10})alkynyl, -(C_3-C_{10})cycloalkyl, -(C_8-C_{14})bicycloalkyl, -(C_8-C_{14})tricycloalkyl, -(C_5-C_{10})cycloalkenyl, -(C_8-C_{14})bicycloalkenyl, -(C_8-C_{14})tricycloalkenyl, -(3- to 7-membered)heterocycle, or -(7- to 10-membered)bicycloheterocycle, each of which is unsubstituted or substituted with one or more R^5 groups; or

(c) -phenyl, -naphthyl, -(C_{14})aryl or -(5- to 10-membered) heteroaryl, each of which is unsubstituted or substituted with one or more R^6 groups;

each R^4 is independently -(C_1–C_6)alkyl, -(C_2–C_6)alkenyl, -(C_2–C_6)alkynyl, -(C_3–C_8)cycloalkyl, -(C_5–C_8)cycloalkenyl, -phenyl, -(3- to 5-membered)heterocycle, -C(halo)$_3$, -CH(halo)$_2$, or CH_2(halo);

each R^5 is independently -CN, -OH, -(C_1–C_6)alkyl, -(C_2–C_6)alkenyl, -(C_2–C_6)alkenyl, -halo, -N_3, -NO_2, -N(R^8)$_2$, -CH=NR^8, -NR^8OH, -OR^8, -COR^8, -C(O)OR^8, -OC(O)R^8, -OC(O)OR^8, -SR^8, -S(O)R^8, or -S(O)$_2$$R^8$;

each R^6 is independently -(C_1–C_6)alkyl, -(C_2–C_6)alkenyl, -(C_2–C_6)alkynyl, -(C_3–C_8)cycloalkyl, -(C_5–C_8)cycloalkenyl, -phenyl, -(3- to 5-membered)heterocycle, -C(halo)$_3$, -CH(halo)$_2$, -CH_2(halo), -CN, -OH, -halo, -N_3, -NO_2, -CH=NR_7, -NR_7OH, -OR_7, -COR_7, -C(O)OR_7, -OC(O)R_7, -OC(O)OR_7, -SR_7, -S(O)R_7, or -S(O)$_2$$R_7$;

each R^7 is independently -H, -(C_1–C_6)alkyl, -(C_2–C_6)alkenyl, -(C_2–C_6)alkynyl, -(C_3–C_8)cycloalkyl, -(C_5–C_8)cycloalkenyl, -phenyl, -(3- to 5-membered)heterocycle, -C(halo)$_3$, -CH(halo)$_2$, or CH_2(halo);

each R^8 is independently -(C_1–C_6)alkyl, -(C_2–C_6)alkenyl, -(C_2–C_6)alkynyl, -(C_3-C_8)cycloalkyl, -(C_5–C_8)cycloalkenyl, -phenyl, -C(halo)$_3$, -CH(halo)$_2$, -CH_2(halo), -CN, -OH, -halo, -N_3, -NO_2, -CH=NR_7, -NR_7OH, -OR_7, -COR_7, -C(O)OR_7, -OC(O)R_7, -OC(O)OR_7, -SR_7, -S(O)R_7, or -S(O)$_2$$R_7$;

each R^{11} is independently -CN, -OH, -$(C_1$–$C_6)$alkyl, -$(C_2$–$C_6)$alkenyl, -halo, -N_3, -NO_2, -$N(R_7)_2$, -CH=NR_7, -NR_7OH, -OR_7, -COR_7, -C(O)OR_7, -OC(O)R_7, -OC(O)OR_7, -SR_7, -S(O)R_7, or -$S(O)_2R_7$;

each halo is independently -F, -Cl, -Br, or -I;

m is 0 or 1;

n is an integer ranging from 0 to 3;

o is an integer ranging from 0 to 4;

p is an integer ranging from 0 to 2;

q is an integer ranging from 0 to 6;

r is an integer ranging from 0 to 5;

s is an integer ranging from 0 to 4; and

t is an integer ranging from 0 to 2.

A compound of formula (I), (Ia), (Ib), (Ic), (II), (IIa), (III), (IIIa), (IIIb), (IIIc), (IV), (IVa), (V), (VI), or (VII), or a pharmaceutically acceptable salt thereof (a "Cyanoiminopiperazine Compound") is useful for treating or preventing pain, UI, an ulcer, IBD, IBS, an addictive disorder, Parkinson's disease, parkinsonism, anxiety, epilepsy, stroke, a seizure, a pruritic condition, psychosis, a cognitive disorder, a memory deficit, restricted brain function, Huntington's chorea, ALS, dementia, retinopathy, a muscle spasm, a migraine, vomiting, dyskinesia, or depression (each being a "Condition") in an animal.

The invention also relates to compositions comprising an effective amount of a Cyanoiminopiperazine Compound and a pharmaceutically acceptable carrier or excipient. The compositions are useful for treating or preventing a Condition in an animal.

The invention further relates to methods for treating a Condition, comprising administering to an animal in need thereof an effective amount of a Cyanoiminopiperazine Compound.

The invention further relates to methods for preventing a Condition, comprising administering to an animal in need thereof an effective amount of a Cyanoiminopiperazine Compound.

The invention still further relates to methods for inhibiting Vanilloid Receptor 1 ("VR1") function in a cell, comprising contacting a cell capable of expressing VR1 with an effective amount of a Cyanoiminopiperazine Compound.

The invention still further relates to methods for inhibiting mGluR5 function in a cell, comprising contacting a cell capable of expressing mGluR5 with an effective amount of a Cyanoiminopiperazine Compound.

The invention still further relates to methods for inhibiting metabotropic glutamate receptor 1 ("mGluR1") function in a cell, comprising contacting a cell capable of expressing mGluR1 with an effective amount of a Cyanoiminopiperazine Compound.

The invention still further relates to a method for preparing a composition, comprising the step of admixing a Cyanoiminopiperazine Compound and a pharmaceutically acceptable carrier or excipient.

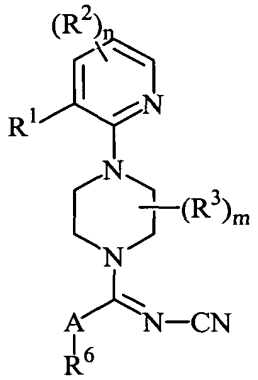
The invention still further relates to a kit comprising a container containing an effective amount of a Cyanoiminopiperazine Compound.

The present invention may be understood more fully by reference to the following detailed description and illustrative examples, which are intended to exemplify non-limiting embodiments of the invention.

4. DETAILED DESCRIPTION OF THE INVENTION

4.1 CYANOIMINOPIPERAZINE COMPOUNDS OF FORMULA (I)

As stated above, the present invention encompasses compounds of Formula (I)



(I)

and pharmaceutically acceptable salts thereof, where A, R^1, R^2, R^3, R^6, n, and m are defined above for the Cyanoiminopiperazine Compounds of formula (I).

In one embodiment n is 0.

In another embodiment, n is 1.

In another embodiment, n is 2.

In another embodiment, n is 3.

In another embodiment, m is 0.

In another embodiment, m is 1.

In another embodiment, m is 2.

In another embodiment, A is -N((C_1-C_6)alkyl)-.

In another embodiment, A is -N(O(C_1-C_6)alkyl)-.

In another embodiment, A is -O-.

In another embodiment, A is -S-.

In another embodiment, R^1 is halo.

In another embodiment, R^1 is -Cl.

In another embodiment, R^1 is -Br.

In another embodiment, R^1 is -I.

In another embodiment, R^1 is -F.

In another embodiment, R^1 is $-CH_3$.

In another embodiment, n is 1 and R^2 is -halo, -CN, -OH, $-NO_2$, or $-NH_2$.

In another embodiment, n is 1 and R^2 is -(C_1-C_{10})alkyl, -(C_2-C_{10})alkenyl, -(C_2-C_{10})alkynyl, -(C_3-C_{10})cycloalkyl, -(C_8-C_{14})bicycloalkyl, -(C_8-C_{14})tricycloalkyl, -(C_5-C_{10})cycloalkenyl,-(C_8-C_{14})bicycloalkenyl, -(C_8-C_{14})tricycloalkenyl, -(C_3-C_7)heterocycle, or -(C_7-C_{10})bicycloheterocycle, each of which is unsubstituted or substituted with one or more R^5 groups.

In another embodiment, n is 1 and R^2 is -phenyl, -naphthyl, -(C_{14})aryl, or -(C_5-C_{10})heteroaryl, each of which is unsubstituted or substituted with one or more R^7 groups;

In another embodiment, m is 1 and R^3 is -halo, -CN, -OH, $-NO_2$, or $-NH_2$.

In another embodiment, m is 1 and R^3 is -(C_1-C_{10})alkyl, -(C_2-C_{10})alkenyl, -(C_2-C_{10})alkynyl, -(C_3-C_{10})cycloalkyl, -(C_8-C_{14})bicycloalkyl, -(C_8-C_{14})tricycloalkyl, -(C_5-C_{10})cycloalkenyl,-(C_8-C_{14})bicycloalkenyl, -(C_8-C_{14})tricycloalkenyl, -(C_3-C_7)heterocycle, or -(C_7-C_{10})bicycloheterocycle, each of which is unsubstituted or substituted with one or more R^5 groups.

In another embodiment, m is 1 and R^3 is -phenyl, -naphthyl, -(C_{14})aryl or -(C_5-C_{10})heteroaryl, each of which is unsubstituted or substituted with one or more R^7 groups.

In another embodiment, R^6 is -phenyl, -naphthyl, -(C_3-C_8)cycloalkyl,-(C_{14})aryl, or -(C_5–C_{10})heteroaryl, each of which is unsubstituted or substituted with one or more R^7 groups.

In another embodiment, R^6 is -phenyl.

In another embodiment, m is 1 and R^3 is -CH_3.

In another embodiment, m is 1, R^3 is -CH_3, and the carbon atom to which the -R^3 is attached is in the (R)-configuration.

In another embodiment, m is 1, R^3 is -CH_3, and the carbon atom to which the -R^3 is attached is in the (S)-configuration.

In one embodiment, n and m are 0 and R^6 is -phenyl. In another embodiment, n is 0, m is 1, R^3 is methyl, and R^6 is phenyl. In another embodiment, the -phenyl is substituted with a -(C_1-C_6) alkyl group. In another embodiment, the -(C_1-C_6) alkyl group is substituted at the 4-position of the -phenyl. In another embodiment, the -(C_1-C_6) alkyl group is a *t*-butyl group substituted at 4-position of the -phenyl. In another embodiment, the -(C_1-C_6) alkyl group is an *iso*-propyl group substituted at the 4-position of the -phenyl.

In another embodiment, R^1 is -CF_3 or -CHF_2.

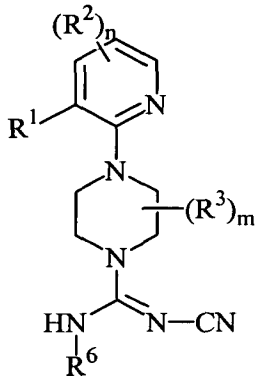
In another embodiment, n and m are 0 and R^6 is -phenyl substituted at its 4-position with a -CF_3 group.

In another embodiment, n and m are 0, R^1 is -halo or methyl; and R^6 is -phenyl. In one embodiment, -halo is -Cl. In another embodiment, the -phenyl is substituted with a -(C_1-C_6) alkyl group. In another embodiment, the -(C_1-C_6) alkyl group is substituted at the 4-position of the -phenyl. In another embodiment, the -(C_1-C_6) alkyl group is a *t*-butyl group or an *iso*-propyl group substituted at the 4-position of the -phenyl.

In another embodiment, n and m are 0, R^1 is -halo or methyl; and R^6 is -phenyl substituted with -CF_3. In another embodiment, -halo is -Cl. In another embodiment, the -CF_3 is substituted at the 4-position of the -phenyl. In another embodiment, -halo is -Cl and the -CF_3 is substituted at the 4-position of the -phenyl.

4.2 CYANOIMINOPIPERAZINE COMPOUNDS OF FORMULA (IA)

The present invention also encompasses compounds of formula (Ia)



(Ia)

and pharmaceutically acceptable salts thereof, wherein R^1, R^2, R^3, R^6, n, and m are defined above for the Cyanoiminopiperazine Compounds of formula (Ia).

In one embodiment, R^1 is -halo.

In another embodiment, R^1 is -Cl.

In another embodiment, R^1 is -Br.

In another embodiment, R^1 is -I.

In another embodiment, R^1 is -F.

In another embodiment, R^1 is $-CH_3$.

In another embodiment, n is 1 and R^2 is -halo, -CN, -OH, $-NO_2$, or $-NH_2$.

In another embodiment, n is 1 and R^2 is $-(C_1\text{-}C_{10})$alkyl, $-(C_2\text{-}C_{10})$alkenyl, $-(C_2\text{-}C_{10})$alkynyl, $-(C_3\text{-}C_{10})$cycloalkyl, $-(C_8\text{-}C_{14})$bicycloalkyl, $-(C_8\text{-}C_{14})$tricycloalkyl, $-(C_5\text{-}C_{10})$cycloalkenyl,$-(C_8\text{-}C_{14})$bicycloalkenyl, $-(C_8\text{-}C_{14})$tricycloalkenyl, $-(C_3\text{-}C_7)$heterocycle, or $-(C_7\text{-}C_{10})$bicycloheterocycle, each of which is unsubstituted or substituted with one or more R^5 groups.

In another embodiment, n is 1 and R^2 is -phenyl, -naphthyl, $-(C_{14})$aryl, or $-(C_5\text{-}C_{10})$heteroaryl, each of which is unsubstituted or substituted with one or more R^7 groups.

In another embodiment, m is 1 and R^3 is -halo, -CN, -OH, $-NO_2$, or $-NH_2$.

In another embodiment, m is 1 and R^3 is $-(C_1\text{-}C_{10})$alkyl, $-(C_2\text{-}C_{10})$alkenyl, $-(C_2\text{-}C_{10})$alkynyl, $-(C_3\text{-}C_{10})$cycloalkyl, $-(C_8\text{-}C_{14})$bicycloalkyl, $-(C_8\text{-}C_{14})$tricycloalkyl, $-(C_5\text{-}C_{10})$cycloalkenyl,$-(C_8\text{-}C_{14})$bicycloalkenyl, $-(C_8\text{-}C_{14})$tricycloalkenyl, $-(C_3\text{-}C_7)$heterocycle, or -

$(C_7$-$C_{10})$bicycloheterocycle, each of which is unsubstituted or substituted with one or more R^5 groups.

In another embodiment, m is 1 and R^3 is -phenyl, -naphthyl, -(C_{14})aryl or -$(C_5$-$C_{10})$heteroaryl, each of which is unsubstituted or substituted with one or more R^7 groups.

In another embodiment, m is 1 and R^3 is -CH_3.

In another embodiment, m is 1, R^3 is -CH_3, and the carbon atom to which the -R^3 is attached is in the (R)-configuration.

In another embodiment, m is 1, R^3 is -CH_3, and the carbon atom to which the -R^3 is attached is in the (S)-configuration.

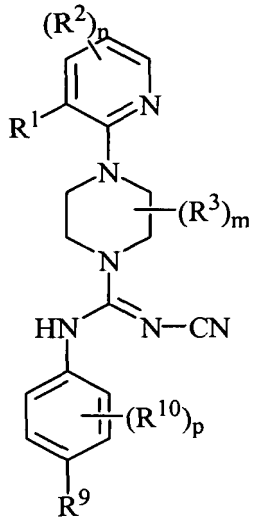
In another embodiment, R^6 is -naphthyl, -(C_{14})aryl, or -$(C_3$-$C_8)$cycloalkyl each of which is unsubstituted or substituted with one or more R^7 groups.

In another embodiment, R^6 is pyridyl, furyl, benzofuranyl, thiophenyl, benzothiophenyl, quinolinyl, indolyl, oxazolyl, benzoxazolyl, imidazolyl, benzimidazolyl, thiazolyl, benzothiazolyl, isoxazolyl, pyrazolyl, isothiazolyl, pyridazinyl, pyrimidinyl, pyrazinyl, thiadiazolyl, triazinyl, cinnolinyl, phthalazinyl, or quinazolinyl, each of which is substituted with one or more R^7 groups.

In another embodiment, R^6 is pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl, or thiadiazolyl.

4.3 CYANOIMINOPIPERAZINE COMPOUNDS OF FORMULA (IB)

The present invention encompasses compounds having the formula (Ib):



(Ib)

and pharmaceutically acceptable salts thereof, wherein R^1, R^2, R^3, R^9, R^{10}, n, m, p and halo are defined above for the Cyanoiminopiperazine Compounds of formula (Ib).

In one embodiment, n is 0.

In another embodiment, n is 1.

In another embodiment, n is 2.

In another embodiment, m is 0.

In another embodiment m is 1.

In another embodiment, m is 2.

In another embodiment, R^1 is -halo.

In another embodiment, R^1 is -Cl.

In another embodiment, R^1 is -Br.

In another embodiment, R^1 is -I.

In another embodiment, R^1 is -F.

In another embodiment, R^1 is $-CH_3$.

In one embodiment, n is 1 and R^2 is -halo, -CN, -OH, $-NO_2$, or $-NH_2$.

In another embodiment, n is 1 and R^2 is $-(C_1\text{-}C_{10})$alkyl, $-(C_2\text{-}C_{10})$alkenyl, $-(C_2\text{-}C_{10})$alkynyl, $-(C_3\text{-}C_{10})$cycloalkyl, $-(C_8\text{-}C_{14})$bicycloalkyl, $-(C_8\text{-}C_{14})$tricycloalkyl, $-(C_5\text{-}C_{10})$cycloalkenyl, $-(C_8\text{-}C_{14})$bicycloalkenyl, $-(C_8\text{-}C_{14})$tricycloalkenyl, $-(C_3\text{-}C_7)$heterocycle, or

-(C_7-C_{10})bicycloheterocycle, each of which is unsubstituted or substituted with one or more R^5 groups.

In another embodiment, n is 1 and R^2 is -phenyl, -naphthyl, -(C_{14})aryl, or -(C_5-C_{10})heteroaryl, each of which is unsubstituted or substituted with one or more R^7 groups.

In another embodiment, m is 1and R^3 is -halo, -CN, -OH, -NO_2, or -NH_2.

In another embodiment, m is 1 and R^3 is-(C_1-C_{10})alkyl, -(C_2-C_{10})alkenyl, -(C_2-C_{10})alkynyl, -(C_3-C_{10})cycloalkyl, -(C_8-C_{14})bicycloalkyl, -(C_8-C_{14})tricycloalkyl, -(C_5-C_{10})cycloalkenyl,-(C_8-C_{14})bicycloalkenyl, -(C_8-C_{14})tricycloalkenyl, -(C_3-C_7)heterocycle, or -(C_7-C_{10})bicycloheterocycle, each of which is unsubstituted or substituted with one or more R^5 groups.

In another embodiment, m is 1 and R^3 is-phenyl, -naphthyl, -(C_{14})aryl or -(C_5-C_{10})heteroaryl, each of which is unsubstituted or substituted with one or more R^7 groups.

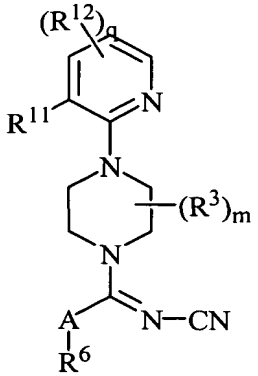
In another embodiment, m is 1 and R^3 is -CH_3.

In another embodiment, m is 1, R^3 is -CH_3, and the carbon atom to which the -R^3 is attached is in the (R)-configuration.

In another embodiment, m is 1, R^3 is -CH_3, and the carbon atom to which the -R^3 is attached is in the (S)-configuration.

4.4 CYANOIMINOPIPERAZINE COMPOUNDS OF FORMULA (IC)

The present invention encompasses compounds having the formula (Ic):



(Ic)

and pharmaceutically acceptable salts thereof, wherein A, R^3, R^6, R^{11}, R^{12}, m, and q are defined above for the Cyanoiminopiperazine Compounds of formula (Ic).

In one embodiment, m is 0.

In another embodiment, m is 1.

In another embodiment, m is 2.

In another embodiment, q is 0.

In another embodiment, q is 1.

In another embodiment, q is 2.

In another embodiment, q is 3.

In another embodiment, A is -N((C_1-C_6)alkyl)-.

In another embodiment, A is -N(O(C_1-C_6)alkyl)-.

In another embodiment, A is -O-.

In another embodiment, A is -S-.

In another embodiment, m is 1 and R^3 is -halo, -CN, -OH, -NO_2, or -NH_2; or

In another embodiment, m is 1 and R^3 is -(C_1-C_{10})alkyl, -(C_2-C_{10})alkenyl, -(C_2-C_{10})alkynyl, -(C_3-C_{10})cycloalkyl, -(C_8-C_{14})bicycloalkyl, -(C_8-C_{14})tricycloalkyl, -(C_5-C_{10})cycloalkenyl,-(C_8-C_{14})bicycloalkenyl, -(C_8-C_{14})tricycloalkenyl, -(C_3-C_7)heterocycle, or -(C_7-C_{10})bicycloheterocycle, each of which is unsubstituted or substituted with one or more R^5 groups.

In another embodiment, m is 1 and R^3 is -phenyl, -naphthyl, -(C_{14})aryl or -(C_5-C_{10})heteroaryl, each of which is unsubstituted or substituted with one or more R^7 groups.

In another embodiment, m is 1 and R^3 is -CH_3.

In another embodiment, m is 1, R^3 is -CH_3, and the carbon atom to which the -R^3 is attached is in the (R)-configuration.

In another embodiment, m is 1, R^3 is -CH_3, and the carbon atom to which the -R^3 is attached is in the (S)-configuration.

In another embodiment, R^6 is -phenyl, -naphthyl, -(C_3-C_8)cycloalkyl,-(C_{14})aryl, or -(C_5–C_{10})heteroaryl, each of which is unsubstituted or substituted with one or more R^7 groups.

In another embodiment, R^6 is -phenyl.

In another embodiment, R^{11} is -hydrogen, -halo, $-CH_3$, $-NO_2$, -CN, -OH, $-OCH_3$, $-NH_2$, $-C(halo)_3$, $-CH(halo)_2$, or $-CH_2(halo)$.

In another embodiment, R^{11} is -halo.

In another embodiment, R^{11} is -Cl.

In another embodiment, R^{11} is -Br.

In another embodiment, R^{11} is -F.

In another embodiment, R^{11} is -I.

In another embodiment, R^{11} is $-CH_3$.

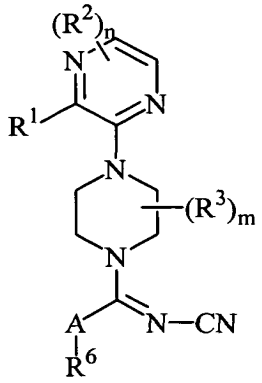
In another embodiment, q is 1 and R^{12} is -halo, -CN, -OH, $-NO_2$, or $-NH_2$.

In another embodiment, q is 1 and R^{12} is $-(C_1-C_{10})$alkyl, $-(C_2-C_{10})$alkenyl, $-(C_2-C_{10})$alkynyl, $-(C_3-C_{10})$cycloalkyl, $-(C_8-C_{14})$bicycloalkyl, $-(C_8-C_{14})$tricycloalkyl, $-(C_5-C_{10})$cycloalkenyl,$-(C_8-C_{14})$bicycloalkenyl, $-(C_8-C_{14})$tricycloalkenyl, $-(C_3-C_7)$heterocycle, or $-(C_7-C_{10})$bicycloheterocycle, each of which is unsubstituted or substituted with one or more R^5 groups.

In one embodiment, q is 1 and R^{12} is -phenyl, -naphthyl, $-(C_{14})$aryl, or $-(C_5-C_{10})$heteroaryl, each of which is unsubstituted or substituted with one or more R^7 groups.

4.5 CYANOIMINOPIPERAZINE COMPOUNDS OF FORMULA (II)

The present invention also encompasses compounds of formula (II)



(II)

and pharmaceutically acceptable salts thereof, wherein A, R^1, R^2, R^3, R^6, n, and m are defined above for the Cyanoiminopiperazine Compounds of formula (II).

In one embodiment, n is 0.

In another embodiment, n is 1.

In another embodiment, n is 2.

In another embodiment, m is 0.

In another embodiment, m is 1.

In another embodiment, m is 2.

In another embodiment, R^1 is -halo.

In another embodiment, R^1 is -Cl.

In another embodiment, R^1 is -Br.

In another embodiment, R^1 is -I.

In another embodiment, R^1 is -F.

In another embodiment, R^1 is $-CH_3$.

In another embodiment, A is -NH-.

In another embodiment, A is $-N((C_1\text{-}C_6)alkyl)-$.

In another embodiment, A is $-N(O(C_1\text{-}C_6)alkyl)-$.

In another embodiment, A is -O-.

In another embodiment, A is -S-.

In another embodiment, n is 1 and R^2 is -halo, -CN, -OH, $-NO_2$, or $-NH_2$.

In another embodiment, n is 1 and R^2 is $-(C_1\text{-}C_{10})alkyl$, $-(C_2\text{-}C_{10})alkenyl$, $-(C_2\text{-}C_{10})alkynyl$, $-(C_3\text{-}C_{10})cycloalkyl$, $-(C_8\text{-}C_{14})bicycloalkyl$, $-(C_8\text{-}C_{14})tricycloalkyl$, $-(C_5\text{-}C_{10})cycloalkenyl$,$-(C_8\text{-}C_{14})bicycloalkenyl$, $-(C_8\text{-}C_{14})tricycloalkenyl$, $-(C_3\text{-}C_7)heterocycle$, or $-(C_7\text{-}C_{10})bicycloheterocycle$, each of which is unsubstituted or substituted with one or more R^5 groups.

In another embodiment, n is 1 and R^2 is -phenyl, -naphthyl, $-(C_{14})aryl$, or $-(C_5\text{-}C_{10})heteroaryl$, each of which is unsubstituted or substituted with one or more R^7 groups.

In another embodiment, m is 1 and R^3 is -halo, -CN, -OH, $-NO_2$, or $-NH_2$.

In another embodiment, m is 1 and R^3 is $-(C_1\text{-}C_{10})alkyl$, $-(C_2\text{-}C_{10})alkenyl$, $-(C_2\text{-}C_{10})alkynyl$, $-(C_3\text{-}C_{10})cycloalkyl$, $-(C_8\text{-}C_{14})bicycloalkyl$, $-(C_8\text{-}C_{14})tricycloalkyl$, $-(C_5\text{-}C_{10})cycloalkenyl$,$-(C_8\text{-}C_{14})bicycloalkenyl$, $-(C_8\text{-}C_{14})tricycloalkenyl$, $-(C_3\text{-}C_7)heterocycle$, or $-(C_7\text{-}C_{10})bicycloheterocycle$, each of which is unsubstituted or substituted with one or more R^5 groups.

In another embodiment, m is 1 and R^3 is -phenyl, -naphthyl, -(C_{14})aryl or -(C_5-C_{10})heteroaryl, each of which is unsubstituted or substituted with one or more R^7 groups.

In another embodiment, m is 1 and R^3 is -CH_3.

In another embodiment, m is 1, R^3 is -CH_3, and the carbon atom to which the -R^3 is attached is in the (R)-configuration.

In another embodiment, m is 1, R^3 is -CH_3, and the carbon atom to which the -R^3 is attached is in the (S)-configuration.

In another embodiment, R^6 is -phenyl, -naphthyl, -(C_3-C_8)cycloalkyl,-(C_{14})aryl, or -(C_5–C_{10})heteroaryl, each of which is unsubstituted or substituted with one or more R^7 groups.

In another embodiment, R^6 is -phenyl.

In one embodiment, n and m are 0 and R^6 is -phenyl. In another embodiment, n is 0, m is 1, R^3 is methyl, and R^6 is phenyl. In another embodiment, the -phenyl is substituted with a -(C_1-C_6) alkyl group. In another embodiment, the -(C_1-C_6) alkyl group is substituted at the 4-position of the -phenyl. In another embodiment, the -(C_1-C_6) alkyl group is a *t*-butyl group substituted at 4-position of the -phenyl. In another embodiment, the -(C_1-C_6) alkyl group is an *iso*-propyl group substituted at the 4-position of the -phenyl.

In another embodiment, R^1 is -CF_3 or -CHF_2.

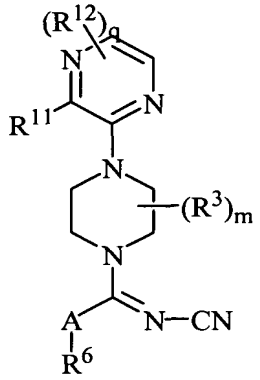
In another embodiment, n and m are 0 and R^6 is -phenyl substituted at its 4-position with a -CF_3 group.

In another embodiment, n and m are 0, R^1 is -halo or methyl; and R^6 is -phenyl. In one embodiment, -halo is -Cl. In another embodiment, the -phenyl is substituted with a -(C_1-C_6) alkyl group. In another embodiment, the -(C_1-C_6) alkyl group is substituted at the 4-position of the -phenyl. In another embodiment, the -(C_1-C_6) alkyl group is a *t*-butyl group or an *iso*-propyl group substituted at the 4-position of the -phenyl.

In another embodiment, n and m are 0, R^1 is -halo or methyl; and R^6 is -phenyl substituted with -CF_3. In another embodiment, -halo is -Cl. In another embodiment, the -CF_3 is substituted at the 4-position of the -phenyl. In another embodiment, -halo is -Cl and the -CF_3 is substituted at the 4-position of the -phenyl.

4.6 CYANOIMINOPIPERAZINE COMPOUNDS OF FORMULA (IIA)

The present invention also encompasses compounds having the formula (IIa):



(IIa)

and pharmaceutically acceptable salts thereof, wherein A, R^3, R^6, R^{11}, R^{12}, m, and q are defined above for the Cyanoiminopiperazine Compounds of formula (IIa).

In one embodiment, q is 0.

In another embodiment q is 1.

In another embodiment q is 2.

In one embodiment, m is 0.

In another embodiment, m is 1.

In another embodiment, m is 2.

In another embodiment, A is -N($(C_1$-$C_6)$alkyl)-.

In another embodiment, A is -N(O(C_1-$C_6)$alkyl)-.

In another embodiment, A is -O-.

In another embodiment, A is -S-.

In another embodiment, m is 1 and R^3 is -halo, -CN, -OH, -NO_2, or -NH_2.

In another embodiment, m is 1 and R^3 is -(C_1-C_{10})alkyl, -(C_2-C_{10})alkenyl, -(C_2-C_{10})alkynyl, -(C_3-C_{10})cycloalkyl, -(C_8-C_{14})bicycloalkyl, -(C_8-C_{14})tricycloalkyl, -(C_5-C_{10})cycloalkenyl,-(C_8-C_{14})bicycloalkenyl, -(C_8-C_{14})tricycloalkenyl, -(C_3-C_7)heterocycle, or -(C_7-C_{10})bicycloheterocycle, each of which is unsubstituted or substituted with one or more R^5 groups.

In another embodiment, m is 1 and R^3 is -phenyl, -naphthyl, -(C_{14})aryl or -(C_5-C_{10})heteroaryl, each of which is unsubstituted or substituted with one or more R^7 groups.

In another embodiment, m is 1 and R^3 is $-CH_3$.

In another embodiment, m is 1, R^3 is $-CH_3$, and the carbon atom to which the $-R^3$ is attached is in the (R)-configuration.

In another embodiment, m is 1, R^3 is $-CH_3$, and the carbon atom to which the $-R^3$ is attached is in the (R)-configuration.

In another embodiment, R^6 is -phenyl, -naphthyl, $-(C_3-C_8)$cycloalkyl,$-(C_{14})$aryl, or $-(C_5-C_{10})$heteroaryl, each of which is unsubstituted or substituted with one or more R^7 groups.

In another embodiment, R^6 is -phenyl.

In another embodiment, R^{11} is -hydrogen, -halo, $-CH_3$, $-NO_2$, -CN, -OH, $-OCH_3$, $-NH_2$, $-C(halo)_3$, $-CH(halo)_2$, or $-CH_2(halo)$.

In another embodiment, R^{11} is -halo.

In another embodiment, R^{11} is -Cl.

In another embodiment, R^{11} is -Br.

In another embodiment, R^{11} is -F.

In another embodiment, R^{11} is -I.

In another embodiment, R^{11} is $-CH_3$.

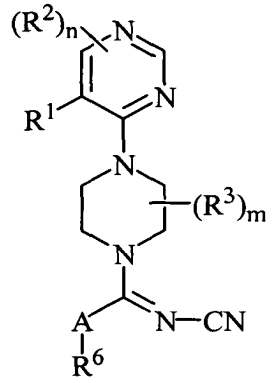
In another embodiment, q is 1 and R^{12} is -halo, -CN, -OH, $-NO_2$, or $-NH_2$.

In another embodiment, q is 1 and R^{12} is $-(C_1-C_{10})$alkyl, $-(C_2-C_{10})$alkenyl, $-(C_2-C_{10})$alkynyl, $-(C_3-C_{10})$cycloalkyl, $-(C_8-C_{14})$bicycloalkyl, $-(C_8-C_{14})$tricycloalkyl, $-(C_5-C_{10})$cycloalkenyl,$-(C_8-C_{14})$bicycloalkenyl, $-(C_8-C_{14})$tricycloalkenyl, $-(C_3-C_7)$heterocycle, or $-(C_7-C_{10})$bicycloheterocycle, each of which is unsubstituted or substituted with one or more R^5 groups.

In another embodiment, q is 1 and R^{12} is -phenyl, -naphthyl, $-(C_{14})$aryl, or $-(C_5-C_{10})$heteroaryl, each of which is unsubstituted or substituted with one or more R^7 groups.

4.7 CYANOIMINOPIPERAZINE COMPOUNDS OF FORMULA (III)

The present invention also encompasses compounds of formula (III)



(III)

and pharmaceutically acceptable salts thereof, wherein A,R^1, R^2, R^3, R^6, m, and nare defined above for the Cyanoiminopiperazine Compounds of formula (III).

In one embodiment, n is 0.

In one embodiment, n is 1.

In one embodiment, n is 2.

In one embodiment, m is 0.

In one embodiment, m is 1.

In one embodiment, m is 2.

In another embodiment, A is -N((C_1-C_6)alkyl)-.

In another embodiment, A is -N(O(C_1-C_6)alkyl)-.

In one embodiment, A is -O-.

In one embodiment, A is -S-.

In one embodiment, R^1 is -halo.

In one embodiment, R^1 is -Cl.

In one embodiment, R^1 is -Br.

In one embodiment, R^1 is -I.

In one embodiment, R^1 is -F.

In one embodiment, R^1 is $-CH_3$.

In one embodiment, n is 1 and R^2 is -halo, -CN, -OH, $-NO_2$, or $-NH_2$.

In one embodiment, n is 1 and R^2 is -(C_1-C_{10})alkyl, -(C_2-C_{10})alkenyl, -(C_2-C_{10})alkynyl, -(C_3-C_{10})cycloalkyl, -(C_8-C_{14})bicycloalkyl, -(C_8-C_{14})tricycloalkyl, -(C_5-C_{10})cycloalkenyl,-(C_8-C_{14})bicycloalkenyl, -(C_8-C_{14})tricycloalkenyl, -(C_3-C_7)heterocycle, or -

$(C_7$-$C_{10})$bicycloheterocycle, each of which is unsubstituted or substituted with one or more R^5 groups.

In one embodiment, n is 1 and R^2 is -phenyl, -naphthyl, -(C_{14})aryl, or -$(C_5$-$C_{10})$heteroaryl, each of which is unsubstituted or substituted with one or more R^7 groups.

In one embodiment, m is 1 and R^3 is -halo, -CN, -OH, $-NO_2$, or $-NH_2$.

In one embodiment, m is 1 and R^3 is -$(C_1$-$C_{10})$alkyl, -$(C_2$-$C_{10})$alkenyl, -$(C_2$-$C_{10})$alkynyl, -$(C_3$-$C_{10})$cycloalkyl, -$(C_8$-$C_{14})$bicycloalkyl, -$(C_8$-$C_{14})$tricycloalkyl, -$(C_5$-$C_{10})$cycloalkenyl,-$(C_8$-$C_{14})$bicycloalkenyl, -$(C_8$-$C_{14})$tricycloalkenyl, -$(C_3$-$C_7)$heterocycle, or -$(C_7$-$C_{10})$bicycloheterocycle, each of which is unsubstituted or substituted with one or more R^5 groups.

In one embodiment, m is 1 and R^3 is -phenyl, -naphthyl, -(C_{14})aryl or -$(C_5$-$C_{10})$heteroaryl, each of which is unsubstituted or substituted with one or more R^7 groups.

In another embodiment, m is 1 and R^3 is $-CH_3$.

In another embodiment, m is 1, R^3 is $-CH_3$, and the carbon atom to which the -R^3 is attached is in the (R)-configuration.

In another embodiment, m is 1, R^3 is $-CH_3$, and the carbon atom to which the -R^3 is attached is in the (S)-configuration.

In one embodiment, R^6 is -phenyl, -naphthyl, -$(C_3$-$C_8)$cycloalkyl,-(C_{14})aryl, or -$(C_5$–$C_{10})$heteroaryl, each of which is unsubstituted or substituted with one or more R^7 groups.

In one embodiment, R^6 is -phenyl.

In one embodiment, n and m are 0 and R^6 is -phenyl. In another embodiment, n is 0, m is 1, R^3 is methyl, and R^6 is phenyl. In another embodiment, the -phenyl is substituted with a -$(C_1$-$C_6)$ alkyl group. In another embodiment, the -$(C_1$-$C_6)$ alkyl group is substituted at the 4-position of the -phenyl. In another embodiment, the -$(C_1$-$C_6)$ alkyl group is a *t*-butyl group substituted at 4-position of the -phenyl. In another embodiment, the -$(C_1$-$C_6)$ alkyl group is an *iso*-propyl group substituted at the 4-position of the -phenyl.

In another embodiment, R^1 is $-CF_3$ or $-CHF_2$.

In another embodiment, n and m are 0 and R^6 is -phenyl substituted at its 4-position with a $-CF_3$ group.

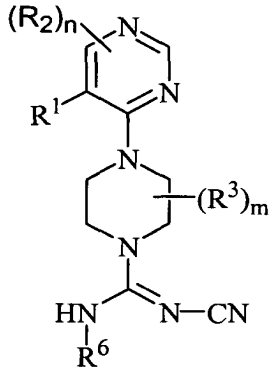
In another embodiment, n and m are 0, R^1 is -halo or methyl; and R^6 is

-phenyl. In one embodiment, -halo is -Cl. In another embodiment, the -phenyl is substituted with a -(C_1-C_6) alkyl group. In another embodiment, the -(C_1-C_6) alkyl group is substituted at the 4-position of the -phenyl. In another embodiment, the -(C_1-C_6) alkyl group is a *t*-butyl group or an *iso*-propyl group substituted at the 4-position of the -phenyl.

In another embodiment, n and m are 0, R^1 is -halo or methyl; and R^6 is -phenyl substituted with -CF_3. In another embodiment, -halo is -Cl. In another embodiment, the -CF_3 is substituted at the 4-position of the -phenyl. In another embodiment, -halo is -Cl and the -CF_3 is substituted at the 4-position of the -phenyl.

4.8 CYANOIMINOPIPERAZINE COMPOUNDS OF FORMULA (IIIA)

The present invention also encompasses compounds of formula (IIIa)



(IIIa)

and pharmaceutically acceptable salts thereof, wherein R^1, R^2, R^3, R^6, n, and m are defined above for the Cyanoiminopiperazine Compounds of formula (IIIa).

In one embodiment, n is 0.

In another embodiment, n is 1.

In another embodiment, n is 2.

In another embodiment, m is 0.

In another embodiment, m is 1.

In another embodiment, m is 2.

In another embodiment, R^1 is -halo.

In another embodiment, R^1 is -Cl.

In another embodiment, R^1 is -Br.

In another embodiment, R^1 is -I.

In another embodiment, R^1 is -F.

In another embodiment, R^1 is $-CH_3$.

In another embodiment, n is 1 and R^2 is -halo, -CN, -OH, $-NO_2$, or $-NH_2$;

In another embodiment, n is 1 and R^2 is $-(C_1-C_{10})$alkyl, $-(C_2-C_{10})$alkenyl, $-(C_2-C_{10})$alkynyl, $-(C_3-C_{10})$cycloalkyl, $-(C_8-C_{14})$bicycloalkyl, $-(C_8-C_{14})$tricycloalkyl, $-(C_5-C_{10})$cycloalkenyl,$-(C_8-C_{14})$bicycloalkenyl, $-(C_8-C_{14})$tricycloalkenyl, $-(C_3-C_7)$heterocycle, or $-(C_7-C_{10})$bicycloheterocycle, each of which is unsubstituted or substituted with one or more R^5 groups; or

In another embodiment, n is 1 and R^2 is -phenyl, -naphthyl, $-(C_{14})$aryl, or $-(C_5-C_{10})$heteroaryl, each of which is unsubstituted or substituted with one or more R^7 groups;

In another embodiment, m is 1 and R^3 is -halo, -CN, -OH, $-NO_2$, or $-NH_2$; or

In another embodiment, m is 1 and R^3 is $-(C_1-C_{10})$alkyl, $-(C_2-C_{10})$alkenyl, $-(C_2-C_{10})$alkynyl, $-(C_3-C_{10})$cycloalkyl, $-(C_8-C_{14})$bicycloalkyl, $-(C_8-C_{14})$tricycloalkyl, $-(C_5-C_{10})$cycloalkenyl,$-(C_8-C_{14})$bicycloalkenyl, $-(C_8-C_{14})$tricycloalkenyl, $-(C_3-C_7)$heterocycle, or $-(C_7-C_{10})$bicycloheterocycle, each of which is unsubstituted or substituted with one or more R^5 groups; or

In another embodiment, m is 1 and R^3 is -phenyl, -naphthyl, $-(C_{14})$aryl or $-(C_5-C_{10})$heteroaryl, each of which is unsubstituted or substituted with one or more R^7 groups.

In another embodiment, m is 1 and R^3 is $-CH_3$.

In another embodiment, m is 1, R^3 is $-CH_3$, and the carbon atom to which the $-R^3$ is attached is in the (R)-configuration.

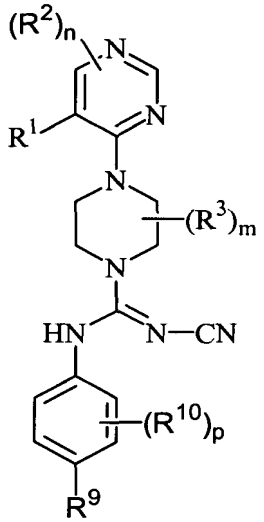
In another embodiment, m is 1, R^3 is $-CH_3$, and the carbon atom to which the $-R^3$ is attached is in the (S)-configuration.

In another embodiment, R^6 is -naphthyl, $-(C_{14})$aryl, or $-(C_3-C_8)$cycloalkyl each of which is unsubstituted or substituted with one or more R^7 groups.

In another embodiment, R^6 is pyridyl, furyl, benzofuranyl, thiophenyl, benzothiophenyl, quinolinyl, indolyl, oxazolyl, benzoxazolyl, imidazolyl, benzimidazolyl, thiazolyl, benzothiazolyl, isoxazolyl, pyrazolyl, isothiazolyl, pyridazinyl, pyrimidinyl, pyrazinyl, thiadiazolyl, triazinyl, cinnolinyl, phthalazinyl, or quinazolinyl, each of which is substituted with one or more R^7 groups.

4.9 CYANOIMINOPIPERAZINE COMPOUNDS OF FORMULA (IIIB)

The present invention encompasses compounds having the formula (IIIb):



(IIIb)

and pharmaceutically acceptable salts thereof, wherein R^1, R^2, R^3, R^9, R^{10}, n, m, and p are defined above for the Cyanoiminopiperazine Compounds of formula (IIIb).

In one embodiment, n is 0.

In another embodiment, n is 1.

In another embodiment, n is 2.

In one embodiment, m is 0.

In another embodiment, m is 1.

In another embodiment, m is 2.

In one embodiment, p is 0.

In another embodiment, p is 1.

In another embodiment, p is 2.

In another embodiment, p is 3.

In another embodiment, p is 4.

In another embodiment, R^1 is -halo.

In another embodiment, R^1 is -Cl.

In another embodiment, R^1 is -Br.

In another embodiment, R^1 is -I.

In another embodiment, R^1 is -F.

In another embodiment, R^1 is $-CH_3$.

In another embodiment, n is 1 and R^2 is -halo, -CN, -OH, $-NO_2$, or $-NH_2$.

In another embodiment, n is 1 and R^2 is $-(C_1\text{-}C_{10})$alkyl, $-(C_2\text{-}C_{10})$alkenyl, $-(C_2\text{-}C_{10})$alkynyl, $-(C_3\text{-}C_{10})$cycloalkyl, $-(C_8\text{-}C_{14})$bicycloalkyl, $-(C_8\text{-}C_{14})$tricycloalkyl, $-(C_5\text{-}C_{10})$cycloalkenyl,$-(C_8\text{-}C_{14})$bicycloalkenyl, $-(C_8\text{-}C_{14})$tricycloalkenyl, $-(C_3\text{-}C_7)$heterocycle, or $-(C_7\text{-}C_{10})$bicycloheterocycle, each of which is unsubstituted or substituted with one or more R^5 groups.

In another embodiment, n is 1 and R^2 is -phenyl, -naphthyl, $-(C_{14})$aryl, or $-(C_5\text{-}C_{10})$heteroaryl, each of which is unsubstituted or substituted with one or more R^7 groups.

In another embodiment, m is 1 and R^3 is -halo, -CN, -OH, $-NO_2$, or $-NH_2$.

In another embodiment, m is 1 and R^3 is $-(C_1\text{-}C_{10})$alkyl, $-(C_2\text{-}C_{10})$alkenyl, $-(C_2\text{-}C_{10})$alkynyl, $-(C_3\text{-}C_{10})$cycloalkyl, $-(C_8\text{-}C_{14})$bicycloalkyl, $-(C_8\text{-}C_{14})$tricycloalkyl, $-(C_5\text{-}C_{10})$cycloalkenyl,$-(C_8\text{-}C_{14})$bicycloalkenyl, $-(C_8\text{-}C_{14})$tricycloalkenyl, $-(C_3\text{-}C_7)$heterocycle, or $-(C_7\text{-}C_{10})$bicycloheterocycle, each of which is unsubstituted or substituted with one or more R^5 groups.

In another embodiment, m is 1 and R^3 is -phenyl, -naphthyl, $-(C_{14})$aryl or $-(C_5\text{-}C_{10})$heteroaryl, each of which is unsubstituted or substituted with one or more R^7 groups.

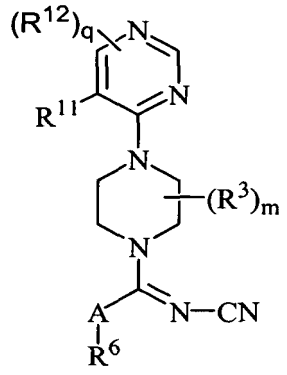
In another embodiment, m is 1 and R^3 is $-CH_3$.

In another embodiment, m is 1, R^3 is $-CH_3$, and the carbon atom to which the $-R^3$ is attached is in the (R)-configuration.

In another embodiment, m is 1, R^3 is $-CH_3$, and the carbon atom to which the $-R^3$ is attached is in the (S)-configuration.

4.10 CYANOIMINOPIPERAZINE COMPOUNDS OF FORMULA (IIIC)

The present invention encompasses compounds having the formula (IIIc):



(IIIc)

and pharmaceutically acceptable salts thereof, wherein A, R^3, R^6, R^{11}, R^{12}, m, and q are defined above for the Cyanoiminopiperazine Compounds of formula (IIIc).

In one embodiment, q is 0.

In another embodiment, q is 1.

In another embodiment, q is 2.

In one embodiment, m is 0.

In another embodiment, m is 1.

In another embodiment, m is 2.

In another embodiment, A is -N($(C_1$-$C_6)$alkyl)-.

In another embodiment, A is -N(O$(C_1$-$C_6)$alkyl)-.

In another embodiment, A is -O-.

In another embodiment, A is -S-.

In another embodiment, m is 1 and R^3 is -halo, -CN, -OH, $-NO_2$, or $-NH_2$.

In another embodiment, m is 1 and R^3 is -$(C_1$-$C_{10})$alkyl, -$(C_2$-$C_{10})$alkenyl, -$(C_2$-$C_{10})$alkynyl, -$(C_3$-$C_{10})$cycloalkyl, -$(C_8$-$C_{14})$bicycloalkyl, -$(C_8$-$C_{14})$tricycloalkyl, -$(C_5$-$C_{10})$cycloalkenyl,-$(C_8$-$C_{14})$bicycloalkenyl, -$(C_8$-$C_{14})$tricycloalkenyl, -$(C_3$-$C_7)$heterocycle, or -$(C_7$-$C_{10})$bicycloheterocycle, each of which is unsubstituted or substituted with one or more R^5 groups.

In another embodiment, m is 1 and R^3 is -phenyl, -naphthyl, -(C_{14})aryl or -$(C_5$-$C_{10})$heteroaryl, each of which is unsubstituted or substituted with one or more R^7 groups.

In another embodiment, m is 1 and R^3 is -CH_3.

In another embodiment, m is 1, R^3 is $-CH_3$, and the carbon atom to which the $-R^3$ is attached is in the (R)-configuration.

In another embodiment, m is 1, R^3 is $-CH_3$, and the carbon atom to which the $-R^3$ is attached is in the (S)-configuration.

In another embodiment, R^6 is -phenyl, -naphthyl, $-(C_3-C_8)$cycloalkyl,$-(C_{14})$aryl, or $-(C_5-C_{10})$heteroaryl, each of which is unsubstituted or substituted with one or more R^7 groups.

In another embodiment, R^6 is -phenyl.

In another embodiment, R^{11} is -hydrogen, -halo, $-CH_3$, $-NO_2$, -CN, -OH, $-OCH_3$, $-NH_2$, $-C(halo)_3$, $-CH(halo)_2$, or $-CH_2(halo)$.

In another embodiment, R^{11} is -halo.

In another embodiment, R^{11} is -Cl.

In another embodiment, R^{11} is -Br.

In another embodiment, R^{11} is -F.

In another embodiment, R^{11} is -I.

In another embodiment, R^{11} is $-CH_3$.

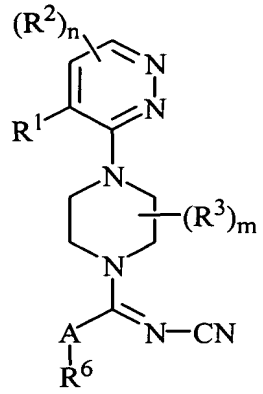
In another embodiment, q is 1 and R^{12} is -halo, -CN, -OH, $-NO_2$, or $-NH_2$.

In another embodiment, q is 1 and R^{12} is $-(C_1-C_{10})$alkyl, $-(C_2-C_{10})$alkenyl, $-(C_2-C_{10})$alkynyl, $-(C_3-C_{10})$cycloalkyl, $-(C_8-C_{14})$bicycloalkyl, $-(C_8-C_{14})$tricycloalkyl, $-(C_5-C_{10})$cycloalkenyl,$-(C_8-C_{14})$bicycloalkenyl, $-(C_8-C_{14})$tricycloalkenyl, $-(C_3-C_7)$heterocycle, or $-(C_7-C_{10})$bicycloheterocycle, each of which is unsubstituted or substituted with one or more R^5 groups.

In another embodiment, q is 1 and R^{12} is -phenyl, -naphthyl, $-(C_{14})$aryl, or $-(C_5-C_{10})$heteroaryl, each of which is unsubstituted or substituted with one or more R^7 groups.

4.11 CYANOIMINOPIPERAZINE COMPOUNDS OF FORMULA (IV)

The present invention also encompasses compounds of formula (IV):



(IV)

and pharmaceutically acceptable salts thereof, where A, R^1, R^2, R^3, R^6, n, and m are defined above for the Cyanoiminopiperazine Compounds of formula (IV).

In one embodiment, n is 0.

In another embodiment, n is 1.

In another embodiment, n is 2.

In one embodiment, m is 0.

In another embodiment, m is 1.

In another embodiment, m is 2.

In another embodiment, A is -NH-.

In another embodiment, A is -N($(C_1$-$C_6)$alkyl)-.

In another embodiment, A is -N(O(C_1-$C_6)$alkyl)-.

In another embodiment, A is -O-.

In another embodiment, A is -S-.

In another embodiment, R^1 is -halo.

In another embodiment, R^1 is -Cl.

In another embodiment, R^1 is -Br.

In another embodiment, R^1 is -I.

In another embodiment, R^1 is -F.

In another embodiment, R^1 is $-CH_3$.

In another embodiment, n is one and R^2 is -halo, -CN, -OH, $-NO_2$, or $-NH_2$;

In another embodiment, n is 1 and R^2 is -(C_1-C_{10})alkyl, -(C_2-C_{10})alkenyl, -(C_2-C_{10})alkynyl, -(C_3-C_{10})cycloalkyl, -(C_8-C_{14})bicycloalkyl, -(C_8-C_{14})tricycloalkyl, -(C_5-

C_{10})cycloalkenyl,-(C_8-C_{14})bicycloalkenyl, -(C_8-C_{14})tricycloalkenyl, -(C_3-C_7)heterocycle, or -(C_7-C_{10})bicycloheterocycle, each of which is unsubstituted or substituted with one or more R^5 groups.

In another embodiment, n is 1 and R^2 is -phenyl, -naphthyl, -(C_{14})aryl, or -(C_5-C_{10})heteroaryl, each of which is unsubstituted or substituted with one or more R^7 groups;

In another embodiment, m is 1 and R^3 is -halo, -CN, -OH, -NO_2, or -NH_2.

In another embodiment, m is 1 and R^3 is -(C_1-C_{10})alkyl, -(C_2-C_{10})alkenyl, -(C_2-C_{10})alkynyl, -(C_3-C_{10})cycloalkyl, -(C_8-C_{14})bicycloalkyl, -(C_8-C_{14})tricycloalkyl, -(C_5-C_{10})cycloalkenyl,-(C_8-C_{14})bicycloalkenyl, -(C_8-C_{14})tricycloalkenyl, -(C_3-C_7)heterocycle, or -(C_7-C_{10})bicycloheterocycle, each of which is unsubstituted or substituted with one or more R^5 groups.

In another embodiment, m is 1 and R^3 is -phenyl, -naphthyl, -(C_{14})aryl or -(C_5-C_{10})heteroaryl, each of which is unsubstituted or substituted with one or more R^7 groups.

In another embodiment, m is 1 and R^3 is -CH_3.

In another embodiment, m is 1, R^3 is -CH_3, and the carbon atom to which the -R^3 is attached is in the (R)-configuration.

In another embodiment, m is 1, R^3 is -CH_3, and the carbon atom to which the -R^3 is attached is in the (S)-configuration.

In another embodiment, R^6 is -phenyl, -naphthyl, -(C_3-C_8)cycloalkyl,-(C_{14})aryl, or -(C_5–C_{10})heteroaryl, each of which is unsubstituted or substituted with one or more R^7 groups.

In another embodiment, R^6 is -phenyl.

In one embodiment, n and m are 0 and R^6 is -phenyl. In another embodiment, n is 0, m is 1, R^3 is methyl, and R^6 is phenyl. In another embodiment, the -phenyl is substituted with a -(C_1-C_6) alkyl group. In another embodiment, the -(C_1-C_6) alkyl group is substituted at the 4-position of the -phenyl. In another embodiment, the -(C_1-C_6) alkyl group is a *t*-butyl group substituted at 4-position of the -phenyl. In another embodiment, the -(C_1-C_6) alkyl group is an *iso*-propyl group substituted at the 4-position of the -phenyl.

In another embodiment, R^1 is -CF_3 or -CHF_2.

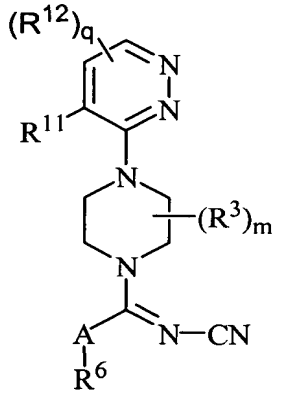
In another embodiment, n and m are 0 and R^6 is -phenyl substituted at its 4-position with a -CF_3 group.

In another embodiment, n and m are 0, R^1 is -halo or methyl; and R^6 is -phenyl. In one embodiment, -halo is -Cl. In another embodiment, the -phenyl is substituted with a -(C_1-C_6) alkyl group. In another embodiment, the -(C_1-C_6) alkyl group is substituted at the 4-position of the -phenyl. In another embodiment, the -(C_1-C_6) alkyl group is a *t*-butyl group or an *iso*-propyl group substituted at the 4-position of the -phenyl.

In another embodiment, n and m are 0, R^1 is -halo or methyl; and R^6 is -phenyl substituted with -CF_3. In another embodiment, -halo is -Cl. In another embodiment, the -CF_3 is substituted at the 4-position of the -phenyl. In another embodiment, -halo is -Cl and the -CF_3 is substituted at the 4-position of the -phenyl.

4.12 CYANOIMINOPIPERAZINE COMPOUNDS OF FORMULA (IVA)

The present invention also encompasses compounds having the formula (IVa):



(IVa)

and pharmaceutically acceptable salts thereof, wherein A, R^3, R^6, R^{11}, R^{12}, m and q are defined above for the Cyanoiminopiperazine Compounds of formula (IVa).

In one embodiment, q is 0.

In another embodiment, q is 1.

In another embodiment, q is 2.

In one embodiment, m is 0.

In another embodiment, m is 1.

In another embodiment, m is 2.

In another embodiment, A is -NH-.

In another embodiment, A is -N((C_1-C_6)alkyl)-.

In another embodiment, A is -N(O(C_1-C_6)alkyl)-.

In another embodiment, A is -O-.

In another embodiment, A is -S-.

In another embodiment, m is 1 and R^3 is -halo, -CN, -OH, -NO_2, or -NH_2.

In another embodiment, m is 1 and R^3 is -(C_1-C_{10})alkyl, -(C_2-C_{10})alkenyl, -(C_2-C_{10})alkynyl, -(C_3-C_{10})cycloalkyl, -(C_8-C_{14})bicycloalkyl, -(C_8-C_{14})tricycloalkyl, -(C_5-C_{10})cycloalkenyl,-(C_8-C_{14})bicycloalkenyl, -(C_8-C_{14})tricycloalkenyl, -(C_3-C_7)heterocycle, or -(C_7-C_{10})bicycloheterocycle, each of which is unsubstituted or substituted with one or more R^5 groups.

In another embodiment, m is 1 and R^3 is -phenyl, -naphthyl, -(C_{14})aryl or -(C_5-C_{10})heteroaryl, each of which is unsubstituted or substituted with one or more R^7 groups.

In another embodiment, m is 1 and R^3 is -CH_3.

In another embodiment, m is 1, R^3 is -CH_3, and the carbon atom to which the -R^3 is attached is in the (R)-configuration.

In another embodiment, m is 1, R^3 is -CH_3, and the carbon atom to which the -R^3 is attached is in the (S)-configuration.

In another embodiment, R^6 is -phenyl, -naphthyl, -(C_3-C_8)cycloalkyl,-(C_{14})aryl, or -(C_5–C_{10})heteroaryl, each of which is unsubstituted or substituted with one or more R^7 groups.

In another embodiment, R^6 is -phenyl.

In another embodiment, R^{11} is -hydrogen, -halo, -CH_3, -NO_2, -CN, -OH, -OCH_3, -NH_2, -C(halo)$_3$, -CH(halo)$_2$, or -CH_2(halo).

In another embodiment, R^{11} is -halo.

In another embodiment, R^{11} is -Cl.

In another embodiment, R^{11} is -Br.

In another embodiment, R^{11} is -F.

In another embodiment, R^{11} is -I.

In another embodiment, R^{11} is -CH_3.

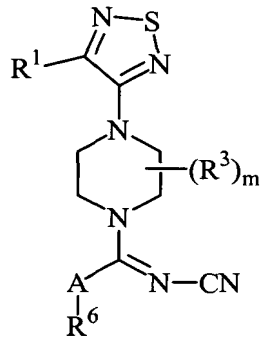
In another embodiment, R^{12} is -halo, -CN, -OH, -NO_2, or -NH_2.

In another embodiment, R^{12} is -(C_1-C_{10})alkyl, -(C_2-C_{10})alkenyl, -(C_2-C_{10})alkynyl, -(C_3-C_{10})cycloalkyl, -(C_8-C_{14})bicycloalkyl, -(C_8-C_{14})tricycloalkyl, -(C_5-C_{10})cycloalkenyl,-(C_8-C_{14})bicycloalkenyl, -(C_8-C_{14})tricycloalkenyl, -(C_3-C_7)heterocycle, or -(C_7-C_{10})bicycloheterocycle, each of which is unsubstituted or substituted with one or more R^5 groups.

In another embodiment, R^{12} is -phenyl, -naphthyl, -(C_{14})aryl, or -(C_5-C_{10})heteroaryl, each of which is unsubstituted or substituted with one or more R^7 groups.

4.13 CYANOIMINOPIPERAZINE COMPOUNDS OF FORMULA (V)

The present invention also encompasses compounds of formula (V)



(V)

and pharmaceutically acceptable salts thereof, wherein A, R^1, R^3, R^6, and m are defined above for the Cyanoiminopiperazine Compounds of formula (V).

In one embodiment, m is 0.

In another embodiment, m is 1.

In another embodiment, m is 2.

In another embodiment, A is -NH-

In another embodiment, A is -N((C_1-C_6)alkyl)-.

In another embodiment, A is -N(O(C_1-C_6)alkyl)-.

In another embodiment, A is -O-.

In another embodiment, A is -S-.

In another embodiment, R^1 is -hydrogen.

In another embodiment, R^1 is -halo, $-CH_3$, $-NO_2$, -CN, -OH, $-OCH_3$, $-NH_2$, $-C(halo)_3$, $-CH(halo)_2$, or $-CH_2(halo)$.

In another embodiment, R^1 is -halo.

In another embodiment, R^1 is -Cl.

In another embodiment, R^1 is -Br.

In another embodiment, R^1 is -I.

In another embodiment, R^1 is -F.

In another embodiment, R^1 is $-CH_3$.

In another embodiment, m is 1 and R^3 is -halo, -CN, -OH, $-NO_2$, or $-NH_2$.

In another embodiment, m is 1 and R^3 is $-(C_1-C_{10})$alkyl, $-(C_2-C_{10})$alkenyl, $-(C_2-C_{10})$alkynyl, $-(C_3-C_{10})$cycloalkyl, $-(C_8-C_{14})$bicycloalkyl, $-(C_8-C_{14})$tricycloalkyl, $-(C_5-C_{10})$cycloalkenyl,$-(C_8-C_{14})$bicycloalkenyl, $-(C_8-C_{14})$tricycloalkenyl, $-(C_3-C_7)$heterocycle, or $-(C_7-C_{10})$bicycloheterocycle, each of which is unsubstituted or substituted with one or more R^5 groups.

In another embodiment, m is 1 and R^3 is -phenyl, -naphthyl, $-(C_{14})$aryl or $-(C_5-C_{10})$heteroaryl, each of which is unsubstituted or substituted with one or more R^7 groups.

In another embodiment, m is 1 and R^3 is $-CH_3$.

In another embodiment, m is 1, R^3 is $-CH_3$, and the carbon atom to which the $-R^3$ is attached is in the (R)-configuration.

In another embodiment, m is 1, R^3 is $-CH_3$, and the carbon atom to which the $-R^3$ is attached is in the (S)-configuration.

In another embodiment, R^6 is -phenyl, -naphthyl, $-(C_3-C_8)$cycloalkyl,$-(C_{14})$aryl, or $-(C_5–C_{10})$heteroaryl, each of which is unsubstituted or substituted with one or more R^7 groups.

In another embodiment, R^6 is -phenyl.

In one embodiment, m is 0 and R^6 is -phenyl. In another embodiment, m is 1, R^3 is methyl, and R^6 is phenyl. In another embodiment, the -phenyl is substituted with a $-(C_1-C_6)$ alkyl group. In another embodiment, the $-(C_1-C_6)$ alkyl group is substituted at the 4-position of the -phenyl. In another embodiment, the $-(C_1-C_6)$ alkyl group is a *t*-butyl group substituted at 4-position of the -phenyl. In another embodiment, the $-(C_1-C_6)$ alkyl group is an *iso*-propyl group substituted at the 4-position of the -phenyl.

In another embodiment, R^1 is $-CF_3$ or $-CHF_2$.

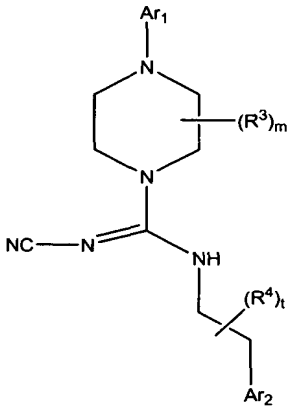
In another embodiment, m is 0 and R^6 is -phenyl substituted at its 4-position with a $-CF_3$ group.

In another embodiment, m is 0, R^1 is -halo or methyl; and R^6 is -phenyl. In one embodiment, -halo is -Cl. In another embodiment, the -phenyl is substituted with a $-(C_1-C_6)$ alkyl group. In another embodiment, the $-(C_1-C_6)$ alkyl group is substituted at the 4-position of the -phenyl. In another embodiment, the $-(C_1-C_6)$ alkyl group is a *t*-butyl group or an *iso*-propyl group substituted at the 4-position of the -phenyl.

In another embodiment, m is 0, R^1 is -halo or methyl; and R^6 is -phenyl substituted with $-CF_3$. In another embodiment, -halo is -Cl. In another embodiment, the $-CF_3$ is substituted at the 4-position of the -phenyl. In another embodiment, -halo is -Cl and the $-CF_3$ is substituted at the 4-position of the -phenyl.

4.14 CYANOIMINOPIPERAZINE COMPOUNDS OF FORMULA (VI)

The present invention also encompasses compounds of formula (VI):



(VI)

and pharmaceutically acceptable salts thereof, wherein Ar_1, Ar_2 R^3, R^4, m, and t are defined above for the Cyanoiminopiperazine Compound of formula (VI).

In one embodiment Ar_1 is a pyridyl group.

In another embodiment, Ar_1 is a pyrimidinyl group.

In another embodiment, Ar_1 is a pyridazinyl group.

In another embodiment, Ar_1 is a pyrazinyl group.

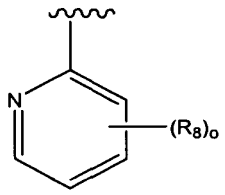
In another embodiment, Ar_1 is a thiadiazolyl group.

In another embodiment, Ar_2 is a benzothiazolyl group.

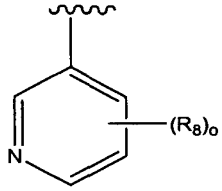
In another embodiment, Ar_2 is a benzoimidazolyl group.

In another embodiment, Ar_2 is a benzooxazolyl group.

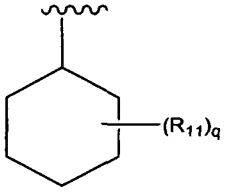
In another embodiment, Ar_2 is



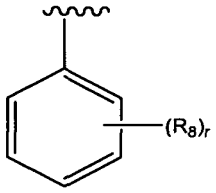
In another embodiment, Ar_2 is



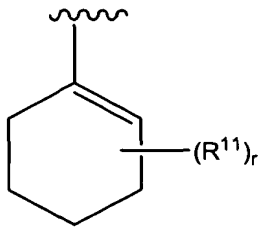
In another embodiment, Ar_2 is



In another embodiment, Ar_2 is

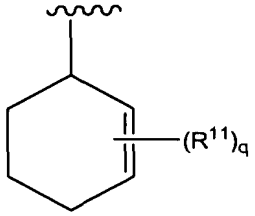


In another embodiment, Ar_2 is



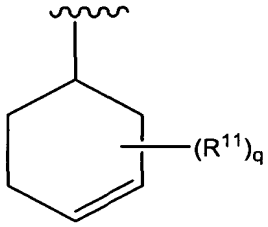
.

In another embodiment, Ar_2 is



.

In another embodiment, Ar_2 is



.

In another embodiment, R_1 is -H.

In another embodiment, R_1 is -halo.

In another embodiment, R_1 is -Cl.

In another embodiment, R_1 is -Br.

In another embodiment, R_1 is -I.

In another embodiment, R_1 is -F.

In another embodiment, R_1 is $-CH_3$.

In another embodiment, R_1 is $-NO_2$.

In another embodiment, R_1 is -CN.

In another embodiment, R_1 is -OH.

In another embodiment, R_1 is $-OCH_3$.

In another embodiment, R_1 is $-NH_2$.

In another embodiment, R_1 is $-C(halo)_3$.

In another embodiment, R_1 is -CH(halo)$_2$.

In another embodiment, R_1 is -CH_2(halo).

In another embodiment, R_2 is -halo, -CN, -OH, -NO_2, or -NH_2.

In another embodiment, R_2 is -(C_1-C_{10})alkyl, -(C_2-C_{10})alkenyl, -(C_2-C_{10})alkynyl, -(C_3-C_{10})cycloalkyl, -(C_8-C_{14})bicycloalkyl, -(C_8-C_{14})tricycloalkyl, -(C_5-C_{10})cycloalkenyl, -(C_8-C_{14})bicycloalkenyl, -(C_8-C_{14})tricycloalkenyl, -(3- to 7-membered)heterocycle, or -(7- to 10-membered)bicycloheterocycle, each of which is unsubstituted or substituted with one or more R_5 groups; or

In another embodiment, R_2 is -phenyl, -naphthyl, -(C_{14})aryl or -(5- to 10-membered)heteroaryl, each of which is unsubstitute or substituted with one or more R_6 groups;

In another embodiment, R_3 is -halo, -CN, -OH, -NO_2, or -NH_2.

In another embodiment, R_3 is -(C_1-C_{10})alkyl, -(C_2-C_{10})alkenyl, -(C_2-C_{10})alkynyl, -(C_3-C_{10})cycloalkyl, -(C_8-C_{14})bicycloalkyl, -(C_8-C_{14})tricycloalkyl, -(C_5-C_{10})cycloalkenyl, -(C_8-C_{14})bicycloalkenyl, -(C_8-C_{14})tricycloalkenyl, -(3- to 7-membered)heterocycle, or -(7- to 10-membered)bicycloheterocycle, each of which is unsubstituted or substituted with one or more R_5 groups.

In another embodiment, R_3 is -phenyl, -naphthyl, -(C_{14})aryl or -(5- to 10-membered) heteroaryl, each of which is unsubstituted or substituted with one or more R_6 groups.

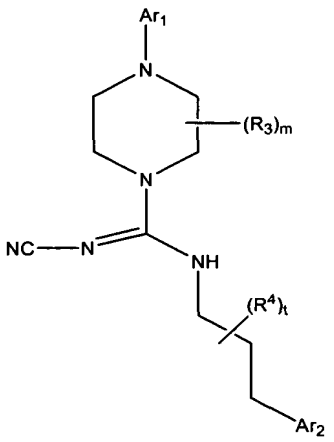
In another embodiment, R_3 is -CH_3.

In another embodiment, m is 1, R^3 is -CH_3, and the carbon atom to which the -R^3 is attached is in the (R)-configuration.

In another embodiment, m is 1, R^3 is -CH_3, and the carbon atom to which the -R^3 is attached is in the (S)-configuration.

4.15 CYANOIMINOPIPERAZINE COMPOUNDS OF FORMULA (VII)

The present invention also encompasses compounds of formula (VII):



(VII)

and pharmaceutically acceptable salts thereof, wherein Ar_1, Ar_2 R_3, R_4, m, and t are defined above for formula (VI).

In one embodiment Ar_1 is a pyridyl group.

In another embodiment, Ar_1 is a pyrimidinyl group.

In another embodiment, Ar_1 is a pyridazinyl group.

In another embodiment, Ar_1 is a pyrazinyl group.

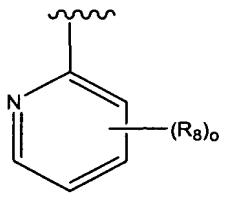
In another embodiment, Ar_1 is a thiadiazolyl group.

In another embodiment, Ar_2 is a benzothiazolyl group.

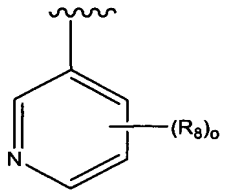
In another embodiment, Ar_2 is a benzoimidazolyl group.

In another embodiment, Ar_2 is a benzooxazolyl group.

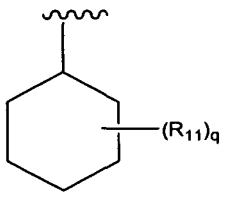
In another embodiment, Ar_2 is



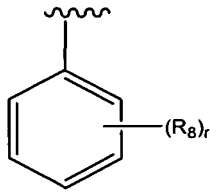
In another embodiment, Ar_2 is



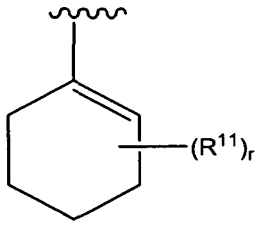
In another embodiment, Ar_2 is



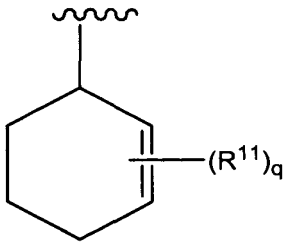
In another embodiment, Ar_2 is



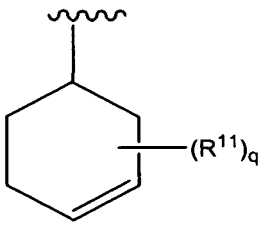
In another embodiment, Ar_2 is



In another embodiment, Ar_2 is



In another embodiment, Ar_2 is



In another embodiment, R_1 is -H.

In another embodiment, R_1 is -halo.

In another embodiment, R_1 is -Cl.

In another embodiment, R_1 is -Br.

In another embodiment, R_1 is -I.

In another embodiment, R_1 is -F.

In another embodiment, R_1 is $-CH_3$.

In another embodiment, R_1 is $-NO_2$.

In another embodiment, R_1 is -CN.

In another embodiment, R_1 is -OH.

In another embodiment, R_1 is $-OCH_3$.

In another embodiment, R_1 is $-NH_2$.

In another embodiment, R_1 is $-C(halo)_3$.

In another embodiment, R_1 is $-CH(halo)_2$.

In another embodiment, R_1 is $-CH_2(halo)$.

In another embodiment, R_2 is -halo, -CN, -OH, $-NO_2$, or $-NH_2$;.

In another embodiment, R_2 is $-(C_1-C_{10})$alkyl, $-(C_2-C_{10})$alkenyl, $-(C_2-C_{10})$alkynyl, $-(C_3-C_{10})$cycloalkyl, $-(C_8-C_{14})$bicycloalkyl, $-(C_8-C_{14})$tricycloalkyl, $-(C_5-C_{10})$cycloalkenyl, $-(C_8-C_{14})$bicycloalkenyl, $-(C_8-C_{14})$tricycloalkenyl, -(3- to 7-membered)heterocycle, or -(7- to 10-membered)bicycloheterocycle, each of which is unsubstituted or substituted with one or more R_5 groups; or

In another embodiment, R_2 is -phenyl, -naphthyl, $-(C_{14})$aryl or -(5- to 10-membered)heteroaryl, each of which is unsubstitute or substituted with one or more R_6 groups;

In another embodiment, R_3 is -halo, -CN, -OH, $-NO_2$, or $-NH_2$.

In another embodiment, R_3 is $-(C_1-C_{10})$alkyl, $-(C_2-C_{10})$alkenyl, $-(C_2-C_{10})$alkynyl, $-(C_3-C_{10})$cycloalkyl, $-(C_8-C_{14})$bicycloalkyl, $-(C_8-C_{14})$tricycloalkyl, $-(C_5-C_{10})$cycloalkenyl, $-(C_8-C_{14})$bicycloalkenyl, $-(C_8-C_{14})$tricycloalkenyl, -(3- to 7-membered)heterocycle, or -(7- to 10-membered)bicycloheterocycle, each of which is unsubstituted or substituted with one or more R_5 groups.

In another embodiment, R_3 is -phenyl, -naphthyl, -(C_{14})aryl or -(5- to 10-membered) heteroaryl, each of which is unsubstituted or substituted with one or more R_6 groups.

In another embodiment, R_3 is -CH_3.

In another embodiment, m is 1, R^3 is -CH_3, and the carbon atom to which the -R^3 is attached is in the (R)-configuration.

In another embodiment, m is 1, R^3 is -CH_3, and the carbon atom to which the -R^3 is attached is in the (S)-configuration.

4.16 CYANOIMINOPIPERAZINE COMPOUNDS OF FORMULA (I), (IA), (IB), (II), (IIA), (III), (IIIA), (IIIB), (IIIC), (IV), (IVA), (V), (VI), AND (VII)

Certain Cyanoiminopiperazine Compounds may have asymmetric centers and therefore exist in different enantiomeric and diastereomic forms. This invention relates to the use of all optical isomers and stereoisomers of the Cyanoiminopiperazine Compounds, and mixtures thereof, and to all pharmaceutical compositions and methods of treatment that may employ or contain them.

In the Cyanoiminopiperazine Compounds each R^3 can be on any carbon of the piperazine ring. In one embodiment, the Cyanoiminopiperazine Compounds have only one R^3 group, and that R^3 group is attached to a carbon atom adjacent to the nitrogen atom attached to the pyridyl, pyrimidinyl, pyrazinyl, pyridazinyl, or thiadiazolyl group. In another embodiment, the Cyanoiminopiperazine Compound has only one R^3 group, and that R^3 group is attached to a carbon atom adjacent to the nitrogen atom attached to the -C(=N-CN)-A-R^6 group, -C(=N-CN)-NH-phenethyl group, -C(=N-CN)-NH-phenpropyl group, or -C(=N-CN)-NH-(R^9)-phenyl.

In another embodiment, two R^3 groups are on a single atom of the piperazine ring. In another embodiment, an R^3 group is attached to a carbon atom adjacent to the nitrogen atom attached to the pyridyl, pyrimidinyl, pyrazinyl, pyridazinyl, or thiadiazolyl group and another R^3 group is attached to a carbon atom adjacent to the nitrogen atom attached to the -C(=N-CN)-A-R^6 group, -C(=N-CN)-NH-phenethyl group, -C(=N-CN)-NH-phenpropyl group, or -C(=N-CN)-NH-(R^9)-phenyl.

In another embodiment, the Cyanoiminopiperazine Compound has two R^3 groups, each being attached to a different carbon atom adjacent to a nitrogen atom attached to

the pyridyl, pyrimidinyl, pyrazinyl, pyridazinyl, or thiadiazolyl group. In another embodiment, the Cyanoiminopiperazine Compound has two R^3 groups, each being attached to a different carbon atom adjacent to a nitrogen atom attached to the -C(=N-CN)-A-R^6 group, -C(=N-CN)-NH-phenethyl group, -C(=N-CN)-NH-phenpropyl group, or -C(=N-CN)-NH-(R^9)-phenyl.

In one embodiment, wherein the Cyanoiminopiperazine Compound has one or two R^3 groups, the carbon atom to which an R^3 group is attached has the (R) configuration. In another embodiment, wherein the Cyanoiminopiperazine Compound has one or two R^3 groups, the carbon atom to which the R^3 group is attached has the (S) configuration. In another embodiment, the Cyanoiminopiperazine Compound has one or two R^3 groups, and at least one of the carbon atoms to which an R^3 group is attached has the (R) configuration. In another embodiment, the Cyanoiminopiperazine Compound has one or two R^3 groups, and at least one of the carbon atoms to which an R^3 group is attached has the (S) configuration.

In another embodiment, the Cyanoiminopiperazine Compound has one or two R^3 groups, an R^3 group is attached to a carbon atom adjacent to a nitrogen atom attached to the pyridyl, pyrimidinyl, pyrazinyl, pyridazinyl, or thiadiazolyl group, and the carbon to which the R^3 group is attached is in the (R) configuration. In another embodiment, the Cyanoiminopiperazine Compound has one or two R^3 groups, an R^3 group is attached to a carbon atom adjacent to a nitrogen attached to the pyridyl, pyrimidinyl, pyrazinyl, pyridazinyl, or thiadiazolyl group, the carbon to which the R^3 group is attached is in the (R) configuration, and R^3 is -(C_1-C_4)alkyl unsubstituted or substituted with one or more halo groups. In another embodiment, the Cyanoiminopiperazine Compound has one or two R^3 groups, an R^3 group is attached to a carbon atom adjacent to a nitrogen attached to the pyridyl, pyrimidinyl, pyrazinyl, pyridazinyl, or thiadiazolyl group, the carbon to which the R^3 group is attached is in the (R) configuration, and R^3 is -CH_3. In another embodiment, the Cyanoiminopiperazine Compound has one or two R^3 groups, an R^3 group is attached to a carbon atom adjacent to a nitrogen attached to the pyridyl, pyrimidinyl, pyrazinyl, pyridazinyl, or thiadiazolyl group, the carbon to which the R^3 group is attached is in the (R) configuration, and R^3 is -CF_3. In another embodiment, the Cyanoiminopiperazine Compound has one or two R^3 groups, an R^3 group is attached to a carbon atom adjacent to a nitrogen

attached to the pyridyl, pyrimidinyl, pyrazinyl, pyridazinyl, or thiadiazolyl group, the carbon to which the R^3 group is attached is in the (R) configuration, and R^3 is $-CH_2CH_3$.

In another embodiment, the Cyanoiminopiperazine Compound has one or two R^3 groups, an R^3 group is attached to a carbon atom adjacent to a nitrogen atom attached to the -C(=N-CN)-A-R^6 group, -C(=N-CN)-NH-phenethyl group, -C(=N-CN)-NH-phenpropyl group, or -C(=N-CN)-NH-(R^9)-phenyl, and the carbon to which the R^3 group is attached is in the (R) configuration. In another embodiment, the Cyanoiminopiperazine Compound has one or two R^3 groups, an R^3 group is attached to a carbon atom adjacent to a nitrogen attached to the -C(=N-CN)-A-R^6 group,-C(=N-CN)-NH-phenethyl group, -C(=N-CN)-NH-phenpropyl group, or -C(=N-CN)-NH-(R^9)-phenyl, the carbon to which the R^3 group is attached is in the (R) configuration, and R^3 is -(C_1-C_4)alkyl unsubstituted or substituted with one or more halo groups. In another embodiment, the Cyanoiminopiperazine Compound has one or two R^3 groups, an R^3 group is attached to a carbon atom adjacent to a nitrogen attached to the -C(=N-CN)-A-R^6 group, -C(=N-CN)-NH-phenethyl group, -C(=N-CN)-NH-phenpropyl group, or -C(=N-CN)-NH-(R^9)-phenyl, the carbon to which the R^3 group is attached is in the (R) configuration, and R^3 is $-CH_3$. In another embodiment, the Cyanoiminopiperazine Compound has one or two R^3 groups, an R^3 group is attached to a carbon atom adjacent to a nitrogen attached to the -C(=N-CN)-A-R^6 group, -C(=N-CN)-NH-phenethyl group, -C(=N-CN)-NH-phenpropyl group, or -C(=N-CN)-NH-(R^9)-phenyl, the carbon to which the R^3 group is attached is in the (R) configuration, and R^3 is $-CF_3$. In another embodiment, the Cyanoiminopiperazine Compound has one or two R^3 groups, an R^3 group is attached to a carbon atom adjacent to a nitrogen attached to the -C(=N-CN)-A-R^6 group,-C(=N-CN)-NH-phenethyl group, -C(=N-CN)-NH-phenpropyl group, or -C(=N-CN)-NH-(R^9)-phenyl, the carbon to which the R^3 group is attached is in the (R) configuration, and R^3 is $-CH_2CH_3$.

In another embodiment, the Cyanoiminopiperazine Compound has one or two R^3 groups, an R^3 group is attached to a carbon atom adjacent to a nitrogen atom attached to the pyridyl, pyrimidinyl, pyrazinyl, pyridazinyl, or thiadiazolyl group, and the carbon to which the R^3 group is attached is in the (S) configuration. In another embodiment, the Cyanoiminopiperazine Compound has one or two R^3 groups, an R^3 group is attached to a carbon atom adjacent to a nitrogen attached to the pyridyl, pyrimidinyl, pyrazinyl, pyridazinyl, or thiadiazolyl group, the carbon to which the R^3 group is attached is in the (S)

configuration, and R^3 is -(C_1-C_4)alkyl unsubstituted or substituted with one or more halo groups. In another embodiment, the Cyanoiminopiperazine Compound has one or two R^3 groups, an R^3 group is attached to a carbon atom adjacent to a nitrogen attached to the pyridyl, pyrimidinyl, pyrazinyl, pyridazinyl, or thiadiazolyl group, the carbon to which the R^3 group is attached is in the (S) configuration, and R^3 is -CH_3. In another embodiment, the Cyanoiminopiperazine Compound has one or two R^3 groups, an R^3 group is attached to a carbon atom adjacent to a nitrogen attached to the pyridyl, pyrimidinyl, pyrazinyl, pyridazinyl, or thiadiazolyl group, the carbon to which the R^3 group is attached is in the (S) configuration, and R^3 is -CF_3. In another embodiment, the Cyanoiminopiperazine Compound has one or two R^3 groups, an R^3 group is attached to a carbon atom adjacent to a nitrogen attached to the pyridyl, pyrimidinyl, pyrazinyl, pyridazinyl, or thiadiazolyl group, the carbon to which the R^3 group is attached is in the (S) configuration, and R^3 is -CH_2CH_3.

In another embodiment, the Cyanoiminopiperazine Compound has one or two R^3 groups, an R^3 group is attached to a carbon atom adjacent to a nitrogen atom attached to the -C(=N-CN)-A-R^6 group, -C(=N-CN)-NH-phenethyl group, -C(=N-CN)-NH-phenpropyl group, or -C(=N-CN)-NH-(R^9)-phenyl, and the carbon to which the R^3 group is attached is in the (S) configuration. In another embodiment, the Cyanoiminopiperazine Compound has one or two R^3 groups, an R^3 group is attached to a carbon atom adjacent to a nitrogen attached to the -C(=N-CN)-A-R^6 group, -C(=N-CN)-NH-phenethyl group, -C(=N-CN)-NH-phenpropyl group, or -C(=N-CN)-NH-(R^9)-phenyl, the carbon to which the R^3 group is attached is in the (S) configuration, and R^3 is -(C_1-C_4)alkyl unsubstituted or substituted with one or more halo groups. In another embodiment, the Cyanoiminopiperazine Compound has one or two R^3 groups, an R^3 group is attached to a carbon atom adjacent to a nitrogen attached to the -C(=N-CN)-A-R^6 group, -C(=N-CN)-NH-phenethyl group, -C(=N-CN)-NH-phenpropyl group, or -C(=N-CN)-NH-(R^9)-phenyl, the carbon to which the R^3 group is attached is in the (S) configuration, and R^3 is -CH_3. In another embodiment, the Cyanoiminopiperazine Compound has one or two R^3 groups, an R^3 group is attached to a carbon atom adjacent to a nitrogen attached to the -C(=N-CN)-A-R^6 group, -C(=N-CN)-NH-phenethyl group, -C(=N-CN)-NH-phenpropyl group, or -C(=N-CN)-NH-(R^9)-phenyl, the carbon to which the R^3 group is attached is in the (S) configuration, and R^3 is -CF_3. In another embodiment, the Cyanoiminopiperazine Compound has one or two R^3 groups, an R^3 group is attached to a

carbon atom adjacent to a nitrogen attached to the -C(=N-CN)-A-R^6 group, -C(=N-CN)-NH-phenethyl group, -C(=N-CN)-NH-phenpropyl group, or -C(=N-CN)-NH-(R^9)-phenyl, the carbon to which the R^3 group is attached is in the (S) configuration, and R^3 is $-CH_2CH_3$.

In another embodiment, the Cyanoiminopiperazine Compound has only one R^3 group, the R^3 group is attached to a carbon atom adjacent to a nitrogen atom attached to the pyridyl, pyrimidinyl, pyrazinyl, pyridazinyl, or thiadiazolyl group, and the carbon to which the R^3 group is attached is in the (R) configuration. In another embodiment, the Cyanoiminopiperazine Compound has only one R^3 group, the R^3 group is attached to a carbon atom adjacent to a nitrogen attached to the pyridyl, pyrimidinyl, pyrazinyl, pyridazinyl, or thiadiazolyl group, the carbon to which the R^3 group is attached is in the (R) configuration, and R^3 is -(C_1-C_4)alkyl unsubstituted or substituted with one or more halo groups. In another embodiment, the Cyanoiminopiperazine Compound has only one R^3 group, the R^3 group is attached to a carbon atom adjacent to a nitrogen attached to the pyridyl, pyrimidinyl, pyrazinyl, pyridazinyl, or thiadiazolyl group, the carbon to which the R^3 group is attached is in the (R) configuration, and R^3 is $-CH_3$. In another embodiment, the Cyanoiminopiperazine Compound has only one R^3 group, the R^3 group is attached to a carbon atom adjacent to a nitrogen attached to the pyridyl, pyrimidinyl, pyrazinyl, pyridazinyl, or thiadiazolyl group, the carbon to which the R^3 group is attached is in the (R) configuration, and R^3 is $-CF_3$. In another embodiment, the Cyanoiminopiperazine Compound has only one R^3 group, the R^3 group is attached to a carbon atom adjacent to a nitrogen attached to the pyridyl, pyrimidinyl, pyrazinyl, pyridazinyl, or thiadiazolyl group, the carbon to which the R^3 group is attached is in the (R) configuration, and R^3 is $-CH_2CH_3$.

In another embodiment, the Cyanoiminopiperazine Compound has only one R^3 group, the R^3 group is attached to a carbon atom adjacent to a nitrogen atom attached to the -C(=N-CN)-A-R^6 group, -C(=N-CN)-NH-phenethyl group, -C(=N-CN)-NH-phenpropyl group, or -C(=N-CN)-NH-(R^9)-phenyl, and the carbon to which the R^3 group is attached is in the (R) configuration. In another embodiment, the Cyanoiminopiperazine Compound has only one R^3 group, the R^3 group is attached to a carbon atom adjacent to a nitrogen attached to the -C(=N-CN)-A-R^6 group, -C(=N-CN)-NH-phenethyl group, -C(=N-CN)-NH-phenpropyl group, or -C(=N-CN)-NH-(R^9)-phenyl, the carbon to which the R^3 group is attached is in the (R) configuration, and R^3 is -(C_1-C_4)alkyl unsubstituted or substituted with one or more halo

groups. In another embodiment, the Cyanoiminopiperazine Compound has only one R^3 group, the R^3 group is attached to a carbon atom adjacent to a nitrogen attached to the -C(=N-CN)-A-R^6 group, -C(=N-CN)-NH-phenethyl group, -C(=N-CN)-NH-phenpropyl group, or -C(=N-CN)-NH-(R^9)-phenyl, the carbon to which the R^3 group is attached is in the (R) configuration, and R^3 is -CH_3. In another embodiment, the Cyanoiminopiperazine Compound has only one R^3 group, the R^3 group is attached to a carbon atom adjacent to a nitrogen attached to the -C(=N-CN)-A-R^6 group, -C(=N-CN)-NH-phenethyl group, -C(=N-CN)-NH-phenpropyl group, or -C(=N-CN)-NH-(R^9)-phenyl, the carbon to which the R^3 group is attached is in the (R) configuration, and R^3 is -CF_3. In another embodiment, the Cyanoiminopiperazine Compound has only one R^3 group, the R^3 group is attached to a carbon atom adjacent to a nitrogen attached to the -C(=N-CN)-A-R^6 group, -C(=N-CN)-NH-phenethyl group, -C(=N-CN)-NH-phenpropyl group, or -C(=N-CN)-NH-(R^9)-phenyl, the carbon to which the R^3 group is attached is in the (R) configuration, and R^3 is -CH_2CH_3.

In another embodiment, the Cyanoiminopiperazine Compound has only one R^3 group, the R^3 group is attached to a carbon atom adjacent to a nitrogen atom attached to the pyridyl, pyrimidinyl, pyrazinyl, pyridazinyl, or thiadiazolyl group, and the carbon to which the R^3 group is attached is in the (S) configuration. In another embodiment, the Cyanoiminopiperazine Compound has only one R^3 group, the R^3 group is attached to a carbon atom adjacent to a nitrogen attached to the pyridyl, pyrimidinyl, pyrazinyl, pyridazinyl, or thiadiazolyl group, the carbon to which the R^3 group is attached is in the (S) configuration, and R^3 is -(C_1-C_4)alkyl unsubstituted or substituted with one or more halo groups. In another embodiment, the Cyanoiminopiperazine Compound has only one R^3 group, the R^3 group is attached to a carbon atom adjacent to a nitrogen attached to the pyridyl, pyrimidinyl, pyrazinyl, pyridazinyl, or thiadiazolyl group, the carbon to which the R^3 group is attached is in the (S) configuration, and R^3 is -CH_3. In another embodiment, the Cyanoiminopiperazine Compound has only one R^3 group, the R^3 group is attached to a carbon atom adjacent to a nitrogen attached to the pyridyl, pyrimidinyl, pyrazinyl, pyridazinyl, or thiadiazolyl group, the carbon to which the R^3 group is attached is in the (S) configuration, and R^3 is -CF_3. In another embodiment, the Cyanoiminopiperazine Compound has only one R^3 group, the R^3 group is attached to a carbon atom adjacent to a nitrogen attached to the pyridyl, pyrimidinyl,

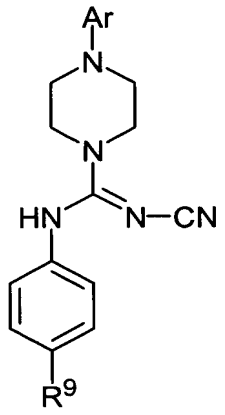
pyrazinyl, pyridazinyl, or thiadiazolyl group, the carbon to which the R^3 group is attached is in the (S) configuration, and R^3 is $-CH_2CH_3$.

In another embodiment, the Cyanoiminopiperazine Compound has only one R^3 group, the R^3 group is attached to a carbon atom adjacent to a nitrogen atom attached to the -C(=N-CN)-A-R^6 group, -C(=N-CN)-NH-phenethyl group, -C(=N-CN)-NH-phenpropyl group, or -C(=N-CN)-NH-(R^9)-phenyl, and the carbon to which the R^3 group is attached is in the (S) configuration. In another embodiment, the Cyanoiminopiperazine Compound has only one R^3 group, the R^3 group is attached to a carbon atom adjacent to a nitrogen attached to the -C(=N-CN)-A-R^6 group, -C(=N-CN)-NH-phenethyl group, -C(=N-CN)-NH-phenpropyl group, or -C(=N-CN)-NH-(R^9)-phenyl, the carbon to which the R^3 group is attached is in the (S) configuration, and R^3 is -(C_1-C_4)alkyl unsubstituted or substituted with one or more halo groups. In another embodiment, the Cyanoiminopiperazine Compound has only one R^3 group, the R^3 group is attached to a carbon atom adjacent to a nitrogen attached to the -C(=N-CN)-A-R^6 group, -C(=N-CN)-NH-phenethyl group, -C(=N-CN)-NH-phenpropyl group, or -C(=N-CN)-NH-(R^9)-phenyl, the carbon to which the R^3 group is attached is in the (S) configuration, and R^3 is $-CH_3$. In another embodiment, the Cyanoiminopiperazine Compound has only one R^3 group, the R^3 group is attached to a carbon atom adjacent to a nitrogen attached to the -C(=N-CN)-A-R^6 group, -C(=N-CN)-NH-phenethyl group, -C(=N-CN)-NH-phenpropyl group, or -C(=N-CN)-NH-(R^9)-phenyl, the carbon to which the R^3 group is attached is in the (S) configuration, and R^3 is $-CF_3$. In another embodiment, the Cyanoiminopiperazine Compound has only one R^3 group, the R^3 group is attached to a carbon atom adjacent to a nitrogen attached to the -C(=N-CN)-A-R^6 group, -C(=N-CN)-NH-phenethyl group, -C(=N-CN)-NH-phenpropyl group, or -C(=N-CN)-NH-(R^9)-phenyl, the carbon to which the R^3 group is attached is in the (R) configuration, and R^3 is $-CH_2CH_3$.

The present invention includes the Cyanoiminopiperazine Compounds, and the pharmaceutically acceptable salts thereof, wherein one or more hydrogen, carbon or other atoms are replaced by isotopes thereof. Such compounds may be useful as research and diagnostic tools in metabolism pharmacokinetic studies and in binding assays.

Illustrative Cyanoiminopiperazine Compounds are listed below in Tables 1-8:

Table 1



VI

and pharmaceutically acceptable salts thereof, wherein:

Compound	Ar	R^9
AAA	-2-(3-chloropyridyl)	-t-butyl
AAB	-2-(3-chloropyridyl)	-iso-butyl
AAC	-2-(3-chloropyridyl)	-sec-butyl
AAD	-2-(3-chloropyridyl)	-cyclohexyl
AAE	-2-(3-chloropyridyl)	-t-butoxy
AAF	-2-(3-chloropyridyl)	-isopropoxy
AAG	-2-(3-chloropyridyl)	$-CF_3$
AAH	-2-(3-chloropyridyl)	$-CH_2CF_3$
AAI	-2-(3-chloropyridyl)	$-OCF_3$
AAJ	-2-(3-chloropyridyl)	-Cl
AAK	-2-(3-chloropyridyl)	-Br
AAL	-2-(3-chloropyridyl)	-I
AAM	-2-(3-chloropyridyl)	-n-butyl
AAN	-2-(3-chloropyridyl)	-n-propyl
AAO	-2-(3-fluoropyridyl)	-t-butyl
AAP	-2-(3-fluoropyridyl)	-iso-butyl

AAQ	-2-(3-fluoropyridyl)	-sec-butyl
AAR	-2-(3-fluoropyridyl)	-cyclohexyl
AAS	-2-(3-fluoropyridyl)	-t-butoxy
AAT	-2-(3-fluoropyridyl)	-isopropoxy
AAU	-2-(3-fluoropyridyl)	$-CF_3$
AAV	-2-(3-fluoropyridyl)	$-CH_2CF_3$
AAW	-2-(3-fluoropyridyl)	$-OCF_3$
AAX	-2-(3-fluoropyridyl)	-Cl
AAY	-2-(3-fluoropyridyl)	-Br
AAZ	-2-(3-fluoropyridyl)	-I
ABA	-2-(3-fluoropyridyl)	-n-butyl
ABB	-2-(3-fluoropyridyl)	-n-propyl
ABC	-2-(3-methylpyridyl)	-t-butyl
ABD	-2-(3-methylpyridyl)	-iso-butyl
ABE	-2-(3-methylpyridyl)	-sec-butyl
ABF	-2-(3-methylpyridyl)	-cyclohexyl
ABG	-2-(3-methylpyridyl)	-t-butoxy
ABH	-2-(3-methylpyridyl)	-isopropoxy
ABI	-2-(3-methylpyridyl)	$-CF_3$
ABJ	-2-(3-methylpyridyl)	$-CH_2CF_3$
ABK	-2-(3-methylpyridyl)	$-OCF_3$
ABL	-2-(3-methylpyridyl)	-Cl
ABM	-2-(3-methylpyridyl)	-Br
ABN	-2-(3-methylpyridyl)	-I
ABO	-2-(3-methylpyridyl)	-n-butyl
ABP	-2-(3-methylpyridyl)	-n-propyl
ABQ	-2-(3-CF_3-pyridyl)	-t-butyl
ABR	-2-(3-CF_3-pyridyl)	-iso-butyl
ABS	-2-(3-CF_3-pyridyl)	-sec-butyl

ABT	-2-(3-CF_3-pyridyl)	-cyclohexyl
ABU	-2-(3-CF_3-pyridyl)	-t-butoxy
ABV	-2-(3-CF_3-pyridyl)	-isopropoxy
ABW	-2-(3-CF_3-pyridyl)	-CF_3
ABX	-2-(3-CF_3-pyridyl)	-CH_2CF_3
ABY	-2-(3-CF_3-pyridyl)	-OCF_3
ABZ	-2-(3-CF_3-pyridyl)	-Cl
ACA	-2-(3-CF_3-pyridyl)	-Br
ACB	-2-(3-CF_3-pyridyl)	-I
ACC	-2-(3-CF_3-pyridyl)	-n-butyl
ACD	-2-(3-CF_3-pyridyl)	-n-propyl
ACE	-2-(3-CHF_2-pyridyl)	-t-butyl
ACF	-2-(3-CHF_2-pyridyl)	-iso-butyl
ACG	-2-(3-CHF_2-pyridyl)	-sec-butyl
ACH	-2-(3-CHF_2-pyridyl)	-cyclohexyl
ACI	-2-(3-CHF_2-pyridyl)	-t-butoxy
ACJ	-2-(3-CHF_2-pyridyl)	-isopropoxy
ACK	-2-(3-CHF_2-pyridyl)	-CF_3
ACL	-2-(3-CHF_2-pyridyl)	-CH_2CF_3
ACM	-2-(3-CHF_2-pyridyl)	-OCF_3
ACN	-2-(3-CHF_2-pyridyl)	-Cl
ACO	-2-(3-CHF_2-pyridyl)	-Br
ACP	-2-(3-CHF_2-pyridyl)	-I
ACQ	-2-(3-CHF_2-pyridyl)	-n-butyl
ACR	-2-(3-CHF_2-pyridyl)	-n-propyl
ACS	-2-(3-hydroxypyridyl)	-t-butyl
ACT	-2-(3-hydroxypyridyl)	-iso-butyl
ACU	-2-(3-hydroxypyridyl)	-sec-butyl
ACV	-2-(3-hydroxypyridyl)	-cyclohexyl

ACW	-2-(3-hydroxypyridyl)	-t-butoxy
ACX	-2-(3-hydroxypyridyl)	-isopropoxy
ACY	-2-(3-hydroxypyridyl)	$-CF_3$
ACZ	-2-(3-hydroxypyridyl)	$-CH_2CF_3$
ADA	-2-(3-hydroxypyridyl)	$-OCF_3$
ADB	-2-(3-hydroxypyridyl)	-Cl
ADC	-2-(3-hydroxypyridyl)	-Br
ADD	-2-(3-hydroxypyridyl)	-I
ADE	-2-(3-hydroxypyridyl)	-n-butyl
ADF	-2-(3-hydroxypyridyl)	-n-propyl
ADG	-2-(3-nitropyridyl)	-t-butyl
ADH	-2-(3-nitropyridyl)	-iso-butyl
ADI	-2-(3-nitropyridyl)	-sec-butyl
ADJ	-2-(3-nitropyridyl)	-cyclohexyl
ADK	-2-(3-nitropyridyl)	-t-butoxy
ADL	-2-(3-nitropyridyl)	-isopropoxy
ADM	-2-(3-nitropyridyl)	$-CF_3$
ADN	-2-(3-nitropyridyl)	$-CH_2CF_3$
ADO	-2-(3-nitropyridyl)	$-OCF_3$
ADP	-2-(3-nitropyridyl)	-Cl
ADQ	-2-(3-nitropyridyl)	-Br
ADR	-2-(3-nitropyridyl)	-I
ADS	-2-(3-nitropyridyl)	-n-butyl
ADT	-2-(3-nitropyridyl)	-n-propyl
ADU	-2-(3-cyanopyridyl)	-t-butyl
ADV	-2-(3-cyanopyridyl)	-iso-butyl
ADW	-2-(3-cyanopyridyl)	-sec-butyl
ADX	-2-(3-cyanopyridyl)	-cyclohexyl
ADY	-2-(3-cyanopyridyl)	-t-butoxy

ADZ	-2-(3-cyanopyridyl)	-isopropoxy
AEA	-2-(3-cyanopyridyl)	$-CF_3$
AEB	-2-(3-cyanopyridyl)	$-CH_2CF_3$
AEC	-2-(3-cyanopyridyl)	$-OCF_3$
AED	-2-(3-cyanopyridyl)	-Cl
AEE	-2-(3-cyanopyridyl)	-Br
AEF	-2-(3-cyanopyridyl)	-I
AEG	-2-(3-cyanopyridyl)	-n-butyl
AEH	-2-(3-cyanopyridyl)	-n-propyl
AEI	-2-(3-bromopyridyl)	-t-butyl
AEJ	-2-(3-bromopyridyl)	-iso-butyl
AEK	-2-(3-bromopyridyl)	-sec-butyl
AEL	-2-(3-bromopyridyl)	-cyclohexyl
AEM	-2-(3-bromopyridyl)	-t-butoxy
AEN	-2-(3-bromopyridyl)	-isopropoxy
AEO	-2-(3-bromopyridyl)	$-CF_3$
AEP	-2-(3-bromopyridyl)	$-CH_2CF_3$
AEQ	-2-(3-bromopyridyl)	$-OCF_3$
AER	-2-(3-bromopyridyl)	-Cl
AES	-2-(3-bromopyridyl)	-Br
AET	-2-(3-bromopyridyl)	-I
AEU	-2-(3-bromopyridyl)	-n-butyl
AEV	-2-(3-bromopyridyl)	-n-propyl
AEW	-2-(3-iodopyridyl)	-t-butyl
AEX	-2-(3-iodopyridyl)	-iso-butyl
AEY	-2-(3-iodopyridyl)	-sec-butyl
AEZ	-2-(3-iodopyridyl)	-cyclohexyl
AFA	-2-(3-iodopyridyl)	-t-butoxy
AFB	-2-(3-iodopyridyl)	-isopropoxy

AFC	-2-(3-iodopyridyl)	$-CF_3$
AFD	-2-(3-iodopyridyl)	$-CH_2CF_3$
AFE	-2-(3-iodopyridyl)	$-OCF_3$
AFF	-2-(3-iodopyridyl)	-Cl
AFG	-2-(3-iodopyridyl)	-Br
AFH	-2-(3-iodopyridyl)	-I
AFI	-2-(3-iodopyridyl)	-n-butyl
AFJ	-2-(3-iodopyridyl)	-n-propyl
AFK	-4-(5-chloropyrimidinyl)	-t-butyl
AFL	-4-(5-chloropyrimidinyl)	-iso-butyl
AFM	-4-(5-chloropyrimidinyl)	-sec-butyl
AFN	-4-(5-chloropyrimidinyl)	-cyclohexyl
AFO	-4-(5-chloropyrimidinyl)	-t-butoxy
AFP	-4-(5-chloropyrimidinyl)	-isopropoxy
AFQ	-4-(5-chloropyrimidinyl)	$-CF_3$
AFR	-4-(5-chloropyrimidinyl)	$-CH_2CF_3$
AFS	-4-(5-chloropyrimidinyl)	$-OCF_3$
AFT	-4-(5-chloropyrimidinyl)	-Cl
AFU	-4-(5-chloropyrimidinyl)	-Br
AFV	-4-(5-chloropyrimidinyl)	-I
AFW	-4-(5-chloropyrimidinyl)	-n-butyl
AFX	-4-(5-chloropyrimidinyl)	-n-propyl
AFY	-4-(5-methylpyrimidinyl)	-t-butyl
AFZ	-4-(5-methylpyrimidinyl)	-iso-butyl
AGA	-4-(5-methylpyrimidinyl)	-sec-butyl
AGB	-4-(5-methylpyrimidinyl)	-cyclohexyl
AGC	-4-(5-methylpyrimidinyl)	-t-butoxy
AGD	-4-(5-methylpyrimidinyl)	-isopropoxy
AGE	-4-(5-methylpyrimidinyl)	$-CF_3$

AGF	-4-(5-methylpyrimidinyl)	$-CH_2CF_3$
AGG	-4-(5-methylpyrimidinyl)	$-OCF_3$
AGH	-4-(5-methylpyrimidinyl)	-Cl
AGI	-4-(5-methylpyrimidinyl)	-Br
AGJ	-4-(5-methylpyrimidinyl)	-I
AGK	-4-(5-methylpyrimidinyl)	-n-butyl
AGL	-4-(5-methylpyrimidinyl)	-n-propyl
AGM	-4-(5-fluoropyrimidinyl)	-t-butyl
AGN	-4-(5-fluoropyrimidinyl)	-iso-butyl
AGO	-4-(5-fluoropyrimidinyl)	-sec-butyl
AGP	-4-(5-fluoropyrimidinyl)	-cyclohexyl
AGQ	-4-(5-fluoropyrimidinyl)	-t-butoxy
AGR	-4-(5-fluoropyrimidinyl)	-isopropoxy
AGS	-4-(5-fluoropyrimidinyl)	$-CF_3$
AGT	-4-(5-fluoropyrimidinyl)	$-CH_2CF_3$
AGU	-4-(5-fluoropyrimidinyl)	$-OCF_3$
AGV	-4-(5-fluoropyrimidinyl)	-Cl
AGW	-4-(5-fluoropyrimidinyl)	-Br
AGX	-4-(5-fluoropyrimidinyl)	-I
AGY	-4-(5-fluoropyrimidinyl)	-n-butyl
AGZ	-4-(5-fluoropyrimidinyl)	-n-propyl
AHA	-2-(3-chloropyrazinyl)	-t-butyl
AHB	-2-(3-chloropyrazinyl)	-iso-butyl
AHC	-2-(3-chloropyrazinyl)	-sec-butyl
AHD	-2-(3-chloropyrazinyl)	-cyclohexyl
AHE	-2-(3-chloropyrazinyl)	-t-butoxy
AHF	-2-(3-chloropyrazinyl)	-isopropoxy
AHG	-2-(3-chloropyrazinyl)	$-CF_3$
AHH	-2-(3-chloropyrazinyl)	$-CH_2CF_3$

AHI	-2-(3-chloropyrazinyl)	$-OCF_3$
AHJ	-2-(3-chloropyrazinyl)	-Cl
AHK	-2-(3-chloropyrazinyl)	-Br
AHL	-2-(3-chloropyrazinyl)	-I
AHM	-2-(3-chloropyrazinyl)	-n-butyl
AHN	-2-(3-chloropyrazinyl)	-n-propyl
AHO	-2-(3-methylpyrazinyl)	-t-butyl
AHP	-2-(3-methylpyrazinyl)	-iso-butyl
AHQ	-2-(3-methylpyrazinyl)	-sec-butyl
AHR	-2-(3-methylpyrazinyl)	-cyclohexyl
AHS	-2-(3-methylpyrazinyl)	-t-butoxy
AHT	-2-(3-methylpyrazinyl)	-isopropoxy
AHU	-2-(3-methylpyrazinyl)	$-CF_3$
AHV	-2-(3-methylpyrazinyl)	$-CH_2CF_3$
AHW	-2-(3-methylpyrazinyl)	$-OCF_3$
AHX	-2-(3-methylpyrazinyl)	-Cl
AHY	-2-(3-methylpyrazinyl)	-Br
AHZ	-2-(3-methylpyrazinyl)	-I
AIA	-2-(3-methylpyrazinyl)	-n-butyl
AIB	-2-(3-methylpyrazinyl)	-n-propyl
AIC	-2-(3-fluoropyrazinyl)	-t-butyl
AID	-2-(3-fluoropyrazinyl)	-iso-butyl
AIE	-2-(3-fluoropyrazinyl)	-sec-butyl
AIF	-2-(3-fluoropyrazinyl)	-cyclohexyl
AIG	-2-(3-fluoropyrazinyl)	-t-butoxy
AIH	-2-(3-fluoropyrazinyl)	-isopropoxy
AII	-2-(3-fluoropyrazinyl)	$-CF_3$
AIJ	-2-(3-fluoropyrazinyl)	$-CH_2CF_3$
AIK	-2-(3-fluoropyrazinyl)	$-OCF_3$

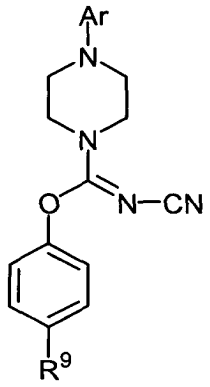
AIL	-2-(3-fluoropyrazinyl)	-Cl
AIM	-2-(3-fluoropyrazinyl)	-Br
AIN	-2-(3-fluoropyrazinyl)	-I
AIO	-2-(3-fluoropyrazinyl)	-n-butyl
AIP	-2-(3-fluoropyrazinyl)	-n-propyl
AIQ	-3-(4-chloropyridazinyl)	-t-butyl
AIR	-3-(4-chloropyridazinyl)	-iso-butyl
AIS	-3-(4-chloropyridazinyl)	-sec-butyl
AIT	-3-(4-chloropyridazinyl)	-cyclohexyl
AIU	-3-(4-chloropyridazinyl)	-t-butoxy
AIV	-3-(4-chloropyridazinyl)	-isopropoxy
AIW	-3-(4-chloropyridazinyl)	$-CF_3$
AIX	-3-(4-chloropyridazinyl)	$-CH_2CF_3$
AIY	-3-(4-chloropyridazinyl)	$-OCF_3$
AIZ	-3-(4-chloropyridazinyl)	-Cl
AJA	-3-(4-chloropyridazinyl)	-Br
AJB	-3-(4-chloropyridazinyl)	-I
AJC	-3-(4-chloropyridazinyl)	-n-butyl
AJD	-3-(4-chloropyridazinyl)	-n-propyl
AJE	-3-(4-methylpyridazinyl)	-t-butyl
AJF	-3-(4-methylpyridazinyl)	-iso-butyl
AJG	-3-(4-methylpyridazinyl)	-sec-butyl
AJH	-3-(4-methylpyridazinyl)	-cyclohexyl
AJI	-3-(4-methylpyridazinyl)	-t-butoxy
AJJ	-3-(4-methylpyridazinyl)	-isopropoxy
AJK	-3-(4-methylpyridazinyl)	$-CF_3$
AJL	-3-(4-methylpyridazinyl)	$-CH_2CF_3$
AJM	-3-(4-methylpyridazinyl)	$-OCF_3$
AJN	-3-(4-methylpyridazinyl)	-Cl

AJO	-3-(4-methylpyridazinyl)	-Br
AJP	-3-(4-methylpyridazinyl)	-I
AJQ	-3-(4-methylpyridazinyl)	-n-butyl
AJR	-3-(4-methylpyridazinyl)	-n-propyl
AJS	-3-(4-fluoropyridazinyl)	-t-butyl
AJT	-3-(4-fluoropyridazinyl)	-iso-butyl
AJU	-3-(4-fluoropyridazinyl)	-sec-butyl
AJV	-3-(4-fluoropyridazinyl)	-cyclohexyl
AJW	-3-(4-fluoropyridazinyl)	-t-butoxy
AJX	-3-(4-fluoropyridazinyl)	-isopropoxy
AJY	-3-(4-fluoropyridazinyl)	$-CF_3$
AJZ	-3-(4-fluoropyridazinyl)	$-CH_2CF_3$
AKA	-3-(4-fluoropyridazinyl)	$-OCF_3$
AKB	-3-(4-fluoropyridazinyl)	-Cl
AKC	-3-(4-fluoropyridazinyl)	-Br
AKD	-3-(4-fluoropyridazinyl)	-I
AKE	-3-(4-fluoropyridazinyl)	-n-butyl
AKF	-3-(4-fluoropyridazinyl)	-n-propyl
AKG	-5-(4-chlorothiadiazolyl)	-t-butyl
AKH	-5-(4-chlorothiadiazolyl)	-iso-butyl
AKI	-5-(4-chlorothiadiazolyl)	-sec-butyl
AKJ	-5-(4-chlorothiadiazolyl)	-cyclohexyl
AKK	-5-(4-chlorothiadiazolyl)	-t-butoxy
AKL	-5-(4-chlorothiadiazolyl)	-isopropoxy
AKM	-5-(4-chlorothiadiazolyl)	$-CF_3$
AKN	-5-(4-chlorothiadiazolyl)	$-CH_2CF_3$
AKO	-5-(4-chlorothiadiazolyl)	$-OCF_3$
AKP	-5-(4-chlorothiadiazolyl)	-Cl
AKQ	-5-(4-chlorothiadiazolyl)	-Br

AKR	-5-(4-chlorothiadiazolyl)	-I
AKS	-5-(4-chlorothiadiazolyl)	-n-butyl
AKT	-5-(4-chlorothiadiazolyl)	-n-propyl
AKU	-5-(4-methylthiadiazolyl)	-t-butyl
AKV	-5-(4-methylthiadiazolyl)	-iso-butyl
AKW	-5-(4-methylthiadiazolyl)	-sec-butyl
AKX	-5-(4-methylthiadiazolyl)	-cyclohexyl
AKY	-5-(4-methylthiadiazolyl)	-t-butoxy
AKZ	-5-(4-methylthiadiazolyl)	-isopropoxy
ALA	-5-(4-methylthiadiazolyl)	$-CF_3$
ALB	-5-(4-methylthiadiazolyl)	$-CH_2CF_3$
ALC	-5-(4-methylthiadiazolyl)	$-OCF_3$
ALD	-5-(4-methylthiadiazolyl)	-Cl
ALE	-5-(4-methylthiadiazolyl)	-Br
ALF	-5-(4-methylthiadiazolyl)	-I
ALG	-5-(4-methylthiadiazolyl)	-n-butyl
ALH	-5-(4-methylthiadiazolyl)	-n-propyl
ALI	-5-(4-fluorothiadiazolyl)	-t-butyl
ALJ	-5-(4-fluorothiadiazolyl)	-iso-butyl
ALK	-5-(4-fluorothiadiazolyl)	-sec-butyl
ALL	-5-(4-fluorothiadiazolyl)	-cyclohexyl
ALM	-5-(4-fluorothiadiazolyl)	-t-butoxy
ALN	-5-(4-fluorothiadiazolyl)	-isopropoxy
ALO	-5-(4-fluorothiadiazolyl)	$-CF_3$
ALP	-5-(4-fluorothiadiazolyl)	$-CH_2CF_3$
ALQ	-5-(4-fluorothiadiazolyl)	$-OCF_3$
ALR	-5-(4-fluorothiadiazolyl)	-Cl
ALS	-5-(4-fluorothiadiazolyl)	-Br
ALT	-5-(4-fluorothiadiazolyl)	-I

ALU	-5-(4-fluorothiadiazolyl)	-n-butyl
ALV	-5-(4-fluorothiadiazolyl)	-n-propyl

Table 2



VII

and pharmaceutically acceptable salts thereof, wherein:

Compound	Ar	R^9
ALW	-2-(3-chloropyridyl)	-t-butyl
ALX	-2-(3-chloropyridyl)	-iso-butyl
ALY	-2-(3-chloropyridyl)	-sec-butyl
ALZ	-2-(3-chloropyridyl)	-cyclohexyl
AMA	-2-(3-chloropyridyl)	-t-butoxy
AMB	-2-(3-chloropyridyl)	-isopropoxy
AMC	-2-(3-chloropyridyl)	$-CF_3$
AMD	-2-(3-chloropyridyl)	$-CH_2CF_3$
AME	-2-(3-chloropyridyl)	$-OCF_3$
AMF	-2-(3-chloropyridyl)	-Cl
AMG	-2-(3-chloropyridyl)	-Br
AMH	-2-(3-chloropyridyl)	-I
AMI	-2-(3-chloropyridyl)	-n-butyl
AMJ	-2-(3-chloropyridyl)	-n-propyl
AMK	-2-(3-fluoropyridyl)	-t-butyl

AML	-2-(3-fluoropyridyl)	-iso-butyl
AMM	-2-(3-fluoropyridyl)	-sec-butyl
AMN	-2-(3-fluoropyridyl)	-cyclohexyl
AMO	-2-(3-fluoropyridyl)	-t-butoxy
AMP	-2-(3-fluoropyridyl)	-isopropoxy
AMQ	-2-(3-fluoropyridyl)	$-CF_3$
AMR	-2-(3-fluoropyridyl)	$-CH_2CF_3$
AMS	-2-(3-fluoropyridyl)	$-OCF_3$
AMT	-2-(3-fluoropyridyl)	-Cl
AMU	-2-(3-fluoropyridyl)	-Br
AMV	-2-(3-fluoropyridyl)	-I
AMW	-2-(3-fluoropyridyl)	-n-butyl
AMX	-2-(3-fluoropyridyl)	-n-propyl
AMY	-2-(3-methylpyridyl)	-t-butyl
AMZ	-2-(3-methylpyridyl)	-iso-butyl
ANA	-2-(3-methylpyridyl)	-sec-butyl
ANB	-2-(3-methylpyridyl)	-cyclohexyl
ANC	-2-(3-methylpyridyl)	-t-butoxy
AND	-2-(3-methylpyridyl)	-isopropoxy
ANE	-2-(3-methylpyridyl)	$-CF_3$
ANF	-2-(3-methylpyridyl)	$-CH_2CF_3$
ANG	-2-(3-methylpyridyl)	$-OCF_3$
ANH	-2-(3-methylpyridyl)	-Cl
ANI	-2-(3-methylpyridyl)	-Br
ANJ	-2-(3-methylpyridyl)	-I
ANK	-2-(3-methylpyridyl)	-n-butyl
ANL	-2-(3-methylpyridyl)	-n-propyl
ANM	-2-(3-CF_3-pyridyl)	-t-butyl
ANN	-2-(3-CF_3-pyridyl)	-iso-butyl

ANO	-2-(3-CF_3-pyridyl)	-sec-butyl
ANP	-2-(3-CF_3-pyridyl)	-cyclohexyl
ANQ	-2-(3-CF_3-pyridyl)	-t-butoxy
ANR	-2-(3-CF_3-pyridyl)	-isopropoxy
ANS	-2-(3-CF_3-pyridyl)	-CF_3
ANT	-2-(3-CF_3-pyridyl)	-CH_2CF_3
ANU	-2-(3-CF_3-pyridyl)	-OCF_3
ANV	-2-(3-CF_3-pyridyl)	-Cl
ANW	-2-(3-CF_3-pyridyl)	-Br
ANX	-2-(3-CF_3-pyridyl)	-I
ANY	-2-(3-CF_3-pyridyl)	-n-butyl
ANZ	-2-(3-CF_3-pyridyl)	-n-propyl
AOA	-2-(3-CHF_2-pyridyl)	-t-butyl
AOB	-2-(3-CHF_2-pyridyl)	-iso-butyl
AOC	-2-(3-CHF_2-pyridyl)	-sec-butyl
AOD	-2-(3-CHF_2-pyridyl)	-cyclohexyl
AOE	-2-(3-CHF_2-pyridyl)	-t-butoxy
AOF	-2-(3-CHF_2-pyridyl)	-isopropoxy
AOG	-2-(3-CHF_2-pyridyl)	-CF_3
AOH	-2-(3-CHF_2-pyridyl)	-CH_2CF_3
AOI	-2-(3-CHF_2-pyridyl)	-OCF_3
AOJ	-2-(3-CHF_2-pyridyl)	-Cl
AOK	-2-(3-CHF_2-pyridyl)	-Br
AOL	-2-(3-CHF_2-pyridyl)	-I
AOM	-2-(3-CHF_2-pyridyl)	-n-butyl
AON	-2-(3-CHF_2-pyridyl)	-n-propyl
AOO	-2-(3-hydroxypyridyl)	-t-butyl
AOP	-2-(3-hydroxypyridyl)	-iso-butyl
AOQ	-2-(3-hydroxypyridyl)	-sec-butyl

AOR	-2-(3-hydroxypyridyl)	-cyclohexyl
AOS	-2-(3-hydroxypyridyl)	-t-butoxy
AOT	-2-(3-hydroxypyridyl)	-isopropoxy
AOU	-2-(3-hydroxypyridyl)	$-CF_3$
AOV	-2-(3-hydroxypyridyl)	$-CH_2CF_3$
AOW	-2-(3-hydroxypyridyl)	$-OCF_3$
AOX	-2-(3-hydroxypyridyl)	-Cl
AOY	-2-(3-hydroxypyridyl)	-Br
AOZ	-2-(3-hydroxypyridyl)	-I
APA	-2-(3-hydroxypyridyl)	-n-butyl
APB	-2-(3-hydroxypyridyl)	-n-propyl
APC	-2-(3-nitropyridyl)	-t-butyl
APD	-2-(3-nitropyridyl)	-iso-butyl
APE	-2-(3-nitropyridyl)	-sec-butyl
APF	-2-(3-nitropyridyl)	-cyclohexyl
APG	-2-(3-nitropyridyl)	-t-butoxy
APH	-2-(3-nitropyridyl)	-isopropoxy
API	-2-(3-nitropyridyl)	$-CF_3$
APJ	-2-(3-nitropyridyl)	$-CH_2CF_3$
APK	-2-(3-nitropyridyl)	$-OCF_3$
APL	-2-(3-nitropyridyl)	-Cl
APM	-2-(3-nitropyridyl)	-Br
APN	-2-(3-nitropyridyl)	-I
APO	-2-(3-nitropyridyl)	-n-butyl
APP	-2-(3-nitropyridyl)	-n-propyl
APQ	-2-(3-cyanopyridyl)	-t-butyl
APR	-2-(3-cyanopyridyl)	-iso-butyl
APS	-2-(3-cyanopyridyl)	-sec-butyl
APT	-2-(3-cyanopyridyl)	-cyclohexyl

APU	-2-(3-cyanopyridyl)	-t-butoxy
APV	-2-(3-cyanopyridyl)	-isopropoxy
APW	-2-(3-cyanopyridyl)	$-CF_3$
APX	-2-(3-cyanopyridyl)	$-CH_2CF_3$
APY	-2-(3-cyanopyridyl)	$-OCF_3$
APZ	-2-(3-cyanopyridyl)	-Cl
AQA	-2-(3-cyanopyridyl)	-Br
AQB	-2-(3-cyanopyridyl)	-I
AQC	-2-(3-cyanopyridyl)	-n-butyl
AQD	-2-(3-cyanopyridyl)	-n-propyl
AQE	-2-(3-bromopyridyl)	-t-butyl
AQF	-2-(3-bromopyridyl)	-iso-butyl
AQG	-2-(3-bromopyridyl)	-sec-butyl
AQH	-2-(3-bromopyridyl)	-cyclohexyl
AQI	-2-(3-bromopyridyl)	-t-butoxy
AQJ	-2-(3-bromopyridyl)	-isopropoxy
AQK	-2-(3-bromopyridyl)	$-CF_3$
AQL	-2-(3-bromopyridyl)	$-CH_2CF_3$
AQM	-2-(3-bromopyridyl)	$-OCF_3$
AQN	-2-(3-bromopyridyl)	-Cl
AQO	-2-(3-bromopyridyl)	-Br
AQP	-2-(3-bromopyridyl)	-I
AQQ	-2-(3-bromopyridyl)	-n-butyl
AQR	-2-(3-bromopyridyl)	-n-propyl
AQS	-2-(3-iodopyridyl)	-t-butyl
AQT	-2-(3-iodopyridyl)	-iso-butyl
AQU	-2-(3-iodopyridyl)	-sec-butyl
AQV	-2-(3-iodopyridyl)	-cyclohexyl
AQW	-2-(3-iodopyridyl)	-t-butoxy

AQX	-2-(3-iodopyridyl)	-isopropoxy
AQY	-2-(3-iodopyridyl)	-CF_3
AQZ	-2-(3-iodopyridyl)	-CH_2CF_3
ARA	-2-(3-iodopyridyl)	-OCF_3
ARB	-2-(3-iodopyridyl)	-Cl
ARC	-2-(3-iodopyridyl)	-Br
ARD	-2-(3-iodopyridyl)	-I
ARE	-2-(3-iodopyridyl)	-n-butyl
ARF	-2-(3-iodopyridyl)	-n-propyl
ARG	-4-(5-chloropyrimidinyl)	-t-butyl
ARH	-4-(5-chloropyrimidinyl)	-iso-butyl
ARI	-4-(5-chloropyrimidinyl)	-sec-butyl
ARJ	-4-(5-chloropyrimidinyl)	-cyclohexyl
ARK	-4-(5-chloropyrimidinyl)	-t-butoxy
ARL	-4-(5-chloropyrimidinyl)	-isopropoxy
ARM	-4-(5-chloropyrimidinyl)	-CF_3
ARN	-4-(5-chloropyrimidinyl)	-CH_2CF_3
ARO	-4-(5-chloropyrimidinyl)	-OCF_3
ARP	-4-(5-chloropyrimidinyl)	-Cl
ARQ	-4-(5-chloropyrimidinyl)	-Br
ARR	-4-(5-chloropyrimidinyl)	-I
ARS	-4-(5-chloropyrimidinyl)	-n-butyl
ART	-4-(5-chloropyrimidinyl)	-n-propyl
ARU	-4-(5-methylpyrimidinyl)	-t-butyl
ARV	-4-(5-methylpyrimidinyl)	-iso-butyl
ARW	-4-(5-methylpyrimidinyl)	-sec-butyl
ARX	-4-(5-methylpyrimidinyl)	-cyclohexyl
ARY	-4-(5-methylpyrimidinyl)	-t-butoxy
ARZ	-4-(5-methylpyrimidinyl)	-isopropoxy

ASA	-4-(5-methylpyrimidinyl)	$-CF_3$
ASB	-4-(5-methylpyrimidinyl)	$-CH_2CF_3$
ASC	-4-(5-methylpyrimidinyl)	$-OCF_3$
ASD	-4-(5-methylpyrimidinyl)	-Cl
ASE	-4-(5-methylpyrimidinyl)	-Br
ASF	-4-(5-methylpyrimidinyl)	-I
ASG	-4-(5-methylpyrimidinyl)	-n-butyl
ASH	-4-(5-methylpyrimidinyl)	-n-propyl
ASI	-4-(5-fluoropyrimidinyl)	-t-butyl
ASJ	-4-(5-fluoropyrimidinyl)	-iso-butyl
ASK	-4-(5-fluoropyrimidinyl)	-sec-butyl
ASL	-4-(5-fluoropyrimidinyl)	-cyclohexyl
ASM	-4-(5-fluoropyrimidinyl)	-t-butoxy
ASN	-4-(5-fluoropyrimidinyl)	-isopropoxy
ASO	-4-(5-fluoropyrimidinyl)	$-CF_3$
ASP	-4-(5-fluoropyrimidinyl)	$-CH_2CF_3$
ASQ	-4-(5-fluoropyrimidinyl)	$-OCF_3$
ASR	-4-(5-fluoropyrimidinyl)	-Cl
ASS	-4-(5-fluoropyrimidinyl)	-Br
AST	-4-(5-fluoropyrimidinyl)	-I
ASU	-4-(5-fluoropyrimidinyl)	-n-butyl
ASV	-4-(5-fluoropyrimidinyl)	-n-propyl
ASW	-2-(3-chloropyrazinyl)	-t-butyl
ASX	-2-(3-chloropyrazinyl)	-iso-butyl
ASY	-2-(3-chloropyrazinyl)	-sec-butyl
ASZ	-2-(3-chloropyrazinyl)	-cyclohexyl
ATA	-2-(3-chloropyrazinyl)	-t-butoxy
ATB	-2-(3-chloropyrazinyl)	-isopropoxy
ATC	-2-(3-chloropyrazinyl)	$-CF_3$

ATD	-2-(3-chloropyrazinyl)	$-CH_2CF_3$
ATE	-2-(3-chloropyrazinyl)	$-OCF_3$
ATF	-2-(3-chloropyrazinyl)	-Cl
ATG	-2-(3-chloropyrazinyl)	-Br
ATH	-2-(3-chloropyrazinyl)	-I
ATI	-2-(3-chloropyrazinyl)	-n-butyl
ATJ	-2-(3-chloropyrazinyl)	-n-propyl
ATK	-2-(3-methylpyrazinyl)	-t-butyl
ATL	-2-(3-methylpyrazinyl)	-iso-butyl
ATM	-2-(3-methylpyrazinyl)	-sec-butyl
ATN	-2-(3-methylpyrazinyl)	-cyclohexyl
ATO	-2-(3-methylpyrazinyl)	-t-butoxy
ATP	-2-(3-methylpyrazinyl)	-isopropoxy
ATQ	-2-(3-methylpyrazinyl)	$-CF_3$
ATR	-2-(3-methylpyrazinyl)	$-CH_2CF_3$
ATS	-2-(3-methylpyrazinyl)	$-OCF_3$
ATT	-2-(3-methylpyrazinyl)	-Cl
ATU	-2-(3-methylpyrazinyl)	-Br
ATV	-2-(3-methylpyrazinyl)	-I
ATW	-2-(3-methylpyrazinyl)	-n-butyl
ATX	-2-(3-methylpyrazinyl)	-n-propyl
ATY	-2-(3-fluoropyrazinyl)	-t-butyl
ATZ	-2-(3-fluoropyrazinyl)	-iso-butyl
AUA	-2-(3-fluoropyrazinyl)	-sec-butyl
AUB	-2-(3-fluoropyrazinyl)	-cyclohexyl
AUC	-2-(3-fluoropyrazinyl)	-t-butoxy
AUD	-2-(3-fluoropyrazinyl)	-isopropoxy
AUE	-2-(3-fluoropyrazinyl)	$-CF_3$
AUF	-2-(3-fluoropyrazinyl)	$-CH_2CF_3$

AUG	-2-(3-fluoropyrazinyl)	-OCF_3
AUH	-2-(3-fluoropyrazinyl)	-Cl
AUI	-2-(3-fluoropyrazinyl)	-Br
AUJ	-2-(3-fluoropyrazinyl)	-I
AUK	-2-(3-fluoropyrazinyl)	-n-butyl
AUL	-2-(3-fluoropyrazinyl)	-n-propyl
AUM	-3-(4-chloropyridazinyl)	-t-butyl
AUN	-3-(4-chloropyridazinyl)	-iso-butyl
AUO	-3-(4-chloropyridazinyl)	-sec-butyl
AUP	-3-(4-chloropyridazinyl)	-cyclohexyl
AUQ	-3-(4-chloropyridazinyl)	-t-butoxy
AUR	-3-(4-chloropyridazinyl)	-isopropoxy
AUS	-3-(4-chloropyridazinyl)	-CF_3
AUT	-3-(4-chloropyridazinyl)	-CH_2CF_3
AUU	-3-(4-chloropyridazinyl)	-OCF_3
AUV	-3-(4-chloropyridazinyl)	-Cl
AUW	-3-(4-chloropyridazinyl)	-Br
AUX	-3-(4-chloropyridazinyl)	-I
AUY	-3-(4-chloropyridazinyl)	-n-butyl
AUZ	-3-(4-chloropyridazinyl)	-n-propyl
AVA	-3-(4-methylpyridazinyl)	-t-butyl
AVB	-3-(4-methylpyridazinyl)	-iso-butyl
AVC	-3-(4-methylpyridazinyl)	-sec-butyl
AVD	-3-(4-methylpyridazinyl)	-cyclohexyl
AVE	-3-(4-methylpyridazinyl)	-t-butoxy
AVF	-3-(4-methylpyridazinyl)	-isopropoxy
AVG	-3-(4-methylpyridazinyl)	-CF_3
AVH	-3-(4-methylpyridazinyl)	-CH_2CF_3
AVI	-3-(4-methylpyridazinyl)	-OCF_3

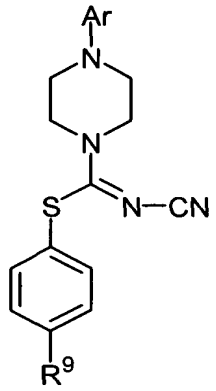
AVJ	-3-(4-methylpyridazinyl)	-Cl
AVK	-3-(4-methylpyridazinyl)	-Br
AVL	-3-(4-methylpyridazinyl)	-I
AVM	-3-(4-methylpyridazinyl)	-n-butyl
AVN	-3-(4-methylpyridazinyl)	-n-propyl
AVO	-3-(4-fluoropyridazinyl)	-t-butyl
AVP	-3-(4-fluoropyridazinyl)	-iso-butyl
AVQ	-3-(4-fluoropyridazinyl)	-sec-butyl
AVR	-3-(4-fluoropyridazinyl)	-cyclohexyl
AVS	-3-(4-fluoropyridazinyl)	-t-butoxy
AVT	-3-(4-fluoropyridazinyl)	-isopropoxy
AVU	-3-(4-fluoropyridazinyl)	$-CF_3$
AVV	-3-(4-fluoropyridazinyl)	$-CH_2CF_3$
AVW	-3-(4-fluoropyridazinyl)	$-OCF_3$
AVX	-3-(4-fluoropyridazinyl)	-Cl
AVY	-3-(4-fluoropyridazinyl)	-Br
AVZ	-3-(4-fluoropyridazinyl)	-I
AWA	-3-(4-fluoropyridazinyl)	-n-butyl
AWB	-3-(4-fluoropyridazinyl)	-n-propyl
AWC	-5-(4-chlorothiadiazolyl)	-t-butyl
AWD	-5-(4-chlorothiadiazolyl)	-iso-butyl
AWE	-5-(4-chlorothiadiazolyl)	-sec-butyl
AWF	-5-(4-chlorothiadiazolyl)	-cyclohexyl
AWG	-5-(4-chlorothiadiazolyl)	-t-butoxy
AWH	-5-(4-chlorothiadiazolyl)	-isopropoxy
AWI	-5-(4-chlorothiadiazolyl)	$-CF_3$
AWJ	-5-(4-chlorothiadiazolyl)	$-CH_2CF_3$
AWK	-5-(4-chlorothiadiazolyl)	$-OCF_3$
AWL	-5-(4-chlorothiadiazolyl)	-Cl

AWM	-5-(4-chlorothiadiazolyl)	-Br
AWN	-5-(4-chlorothiadiazolyl)	-I
AWO	-5-(4-chlorothiadiazolyl)	-n-butyl
AWP	-5-(4-chlorothiadiazolyl)	-n-propyl
AWQ	-5-(4-methylthiadiazolyl)	-t-butyl
AWR	-5-(4-methylthiadiazolyl)	-iso-butyl
AWS	-5-(4-methylthiadiazolyl)	-sec-butyl
AWT	-5-(4-methylthiadiazolyl)	-cyclohexyl
AWU	-5-(4-methylthiadiazolyl)	-t-butoxy
AWV	-5-(4-methylthiadiazolyl)	-isopropoxy
AWW	-5-(4-methylthiadiazolyl)	$-CF_3$
AWX	-5-(4-methylthiadiazolyl)	$-CH_2CF_3$
AWY	-5-(4-methylthiadiazolyl)	$-OCF_3$
AWZ	-5-(4-methylthiadiazolyl)	-Cl
AXA	-5-(4-methylthiadiazolyl)	-Br
AXB	-5-(4-methylthiadiazolyl)	-I
AXC	-5-(4-methylthiadiazolyl)	-n-butyl
AXD	-5-(4-methylthiadiazolyl)	-n-propyl
AXE	-5-(4-fluorothiadiazolyl)	-t-butyl
AXF	-5-(4-fluorothiadiazolyl)	-iso-butyl
AXG	-5-(4-fluorothiadiazolyl)	-sec-butyl
AXH	-5-(4-fluorothiadiazolyl)	-cyclohexyl
AXI	-5-(4-fluorothiadiazolyl)	-t-butoxy
AXJ	-5-(4-fluorothiadiazolyl)	-isopropoxy
AXK	-5-(4-fluorothiadiazolyl)	$-CF_3$
AXL	-5-(4-fluorothiadiazolyl)	$-CH_2CF_3$
AXM	-5-(4-fluorothiadiazolyl)	$-OCF_3$
AXN	-5-(4-fluorothiadiazolyl)	-Cl
AXO	-5-(4-fluorothiadiazolyl)	-Br

AXP	-5-(4-fluorothiadiazolyl)	-I
AXQ	-5-(4-fluorothiadiazolyl)	-n-butyl
AXR	-5-(4-fluorothiadiazolyl)	-n-propyl

5

Table 3



VIII

and pharmaceutically acceptable salts thereof, wherein:

Compound	Ar	R^9
AXS	-2-(3-chloropyridyl)	-t-butyl
AXT	-2-(3-chloropyridyl)	-iso-butyl
AXU	-2-(3-chloropyridyl)	-sec-butyl
AXV	-2-(3-chloropyridyl)	-cyclohexyl
AXW	-2-(3-chloropyridyl)	-t-butoxy
AXX	-2-(3-chloropyridyl)	-isopropoxy
AXY	-2-(3-chloropyridyl)	$-CF_3$
AXZ	-2-(3-chloropyridyl)	$-CH_2CF_3$
AYA	-2-(3-chloropyridyl)	$-OCF_3$
AYB	-2-(3-chloropyridyl)	-Cl
AYC	-2-(3-chloropyridyl)	-Br
AYD	-2-(3-chloropyridyl)	-I
AYE	-2-(3-chloropyridyl)	-n-butyl
AYF	-2-(3-chloropyridyl)	-n-propyl
AYG	-2-(3-fluoropyridyl)	-t-butyl

AYH	-2-(3-fluoropyridyl)	-iso-butyl
AYI	-2-(3-fluoropyridyl)	-sec-butyl
AYJ	-2-(3-fluoropyridyl)	-cyclohexyl
AYK	-2-(3-fluoropyridyl)	-t-butoxy
AYL	-2-(3-fluoropyridyl)	-isopropoxy
AYM	-2-(3-fluoropyridyl)	$-CF_3$
AYN	-2-(3-fluoropyridyl)	$-CH_2CF_3$
AYO	-2-(3-fluoropyridyl)	$-OCF_3$
AYP	-2-(3-fluoropyridyl)	-Cl
AYQ	-2-(3-fluoropyridyl)	-Br
AYR	-2-(3-fluoropyridyl)	-I
AYS	-2-(3-fluoropyridyl)	-n-butyl
AYT	-2-(3-fluoropyridyl)	-n-propyl
AYU	-2-(3-methylpyridyl)	-t-butyl
AYV	-2-(3-methylpyridyl)	-iso-butyl
AYW	-2-(3-methylpyridyl)	-sec-butyl
AYX	-2-(3-methylpyridyl)	-cyclohexyl
AYY	-2-(3-methylpyridyl)	-t-butoxy
AYZ	-2-(3-methylpyridyl)	-isopropoxy
AZA	-2-(3-methylpyridyl)	$-CF_3$
AZB	-2-(3-methylpyridyl)	$-CH_2CF_3$
AZC	-2-(3-methylpyridyl)	$-OCF_3$
AZD	-2-(3-methylpyridyl)	-Cl
AZE	-2-(3-methylpyridyl)	-Br
AZF	-2-(3-methylpyridyl)	-I
AZG	-2-(3-methylpyridyl)	-n-butyl
AZH	-2-(3-methylpyridyl)	-n-propyl
AZI	-2-(3-CF_3-pyridyl)	-t-butyl
AZJ	-2-(3-CF_3-pyridyl)	-iso-butyl

AZK	-2-(3-CF_3-pyridyl)	-sec-butyl
AZL	-2-(3-CF_3-pyridyl)	-cyclohexyl
AZM	-2-(3-CF_3-pyridyl)	-t-butoxy
AZN	-2-(3-CF_3-pyridyl)	-isopropoxy
AZO	-2-(3-CF_3-pyridyl)	-CF_3
AZP	-2-(3-CF_3-pyridyl)	-CH_2CF_3
AZQ	-2-(3-CF_3-pyridyl)	-OCF_3
AZR	-2-(3-CF_3-pyridyl)	-Cl
AZS	-2-(3-CF_3-pyridyl)	-Br
AZT	-2-(3-CF_3-pyridyl)	-I
AZU	-2-(3-CF_3-pyridyl)	-n-butyl
AZV	-2-(3-CF_3-pyridyl)	-n-propyl
AZW	-2-(3-CHF_2-pyridyl)	-t-butyl
AZX	-2-(3-CHF_2-pyridyl)	-iso-butyl
AZY	-2-(3-CHF_2-pyridyl)	-sec-butyl
AZZ	-2-(3-CHF_2-pyridyl)	-cyclohexyl
BAA	-2-(3-CHF_2-pyridyl)	-t-butoxy
BAB	-2-(3-CHF_2-pyridyl)	-isopropoxy
BAC	-2-(3-CHF_2-pyridyl)	-CF_3
BAD	-2-(3-CHF_2-pyridyl)	-CH_2CF_3
BAE	-2-(3-CHF_2-pyridyl)	-OCF_3
BAF	-2-(3-CHF_2-pyridyl)	-Cl
BAG	-2-(3-CHF_2-pyridyl)	-Br
BAH	-2-(3-CHF_2-pyridyl)	-I
BAI	-2-(3-CHF_2-pyridyl)	-n-butyl
BAJ	-2-(3-CHF_2-pyridyl)	-n-propyl
BAK	-2-(3-hydroxypyridyl)	-t-butyl
BAL	-2-(3-hydroxypyridyl)	-iso-butyl
BAM	-2-(3-hydroxypyridyl)	-sec-butyl

BAN	-2-(3-hydroxypyridyl)	-cyclohexyl
BAO	-2-(3-hydroxypyridyl)	-t-butoxy
BAP	-2-(3-hydroxypyridyl)	-isopropoxy
BAQ	-2-(3-hydroxypyridyl)	$-CF_3$
BAR	-2-(3-hydroxypyridyl)	$-CH_2CF_3$
BAS	-2-(3-hydroxypyridyl)	$-OCF_3$
BAT	-2-(3-hydroxypyridyl)	-Cl
BAU	-2-(3-hydroxypyridyl)	-Br
BAV	-2-(3-hydroxypyridyl)	-I
BAW	-2-(3-hydroxypyridyl)	-n-butyl
BAX	-2-(3-hydroxypyridyl)	-n-propyl
BAY	-2-(3-nitropyridyl)	-t-butyl
BAZ	-2-(3-nitropyridyl)	-iso-butyl
BBA	-2-(3-nitropyridyl)	-sec-butyl
BBB	-2-(3-nitropyridyl)	-cyclohexyl
BBC	-2-(3-nitropyridyl)	-t-butoxy
BBD	-2-(3-nitropyridyl)	-isopropoxy
BBE	-2-(3-nitropyridyl)	$-CF_3$
BBF	-2-(3-nitropyridyl)	$-CH_2CF_3$
BBG	-2-(3-nitropyridyl)	$-OCF_3$
BBH	-2-(3-nitropyridyl)	-Cl
BBI	-2-(3-nitropyridyl)	-Br
BBJ	-2-(3-nitropyridyl)	-I
BBK	-2-(3-nitropyridyl)	-n-butyl
BBL	-2-(3-nitropyridyl)	-n-propyl
BBM	-2-(3-cyanopyridyl)	-t-butyl
BBN	-2-(3-cyanopyridyl)	-iso-butyl
BBO	-2-(3-cyanopyridyl)	-sec-butyl
BBP	-2-(3-cyanopyridyl)	-cyclohexyl

BBQ	-2-(3-cyanopyridyl)	-t-butoxy
BBR	-2-(3-cyanopyridyl)	-isopropoxy
BBS	-2-(3-cyanopyridyl)	$-CF_3$
BBT	-2-(3-cyanopyridyl)	$-CH_2CF_3$
BBU	-2-(3-cyanopyridyl)	$-OCF_3$
BBV	-2-(3-cyanopyridyl)	-Cl
BBW	-2-(3-cyanopyridyl)	-Br
BBX	-2-(3-cyanopyridyl)	-I
BBY	-2-(3-cyanopyridyl)	-n-butyl
BBZ	-2-(3-cyanopyridyl)	-n-propyl
BCA	-2-(3-bromopyridyl)	-t-butyl
BCB	-2-(3-bromopyridyl)	-iso-butyl
BCC	-2-(3-bromopyridyl)	-sec-butyl
BCD	-2-(3-bromopyridyl)	-cyclohexyl
BCE	-2-(3-bromopyridyl)	-t-butoxy
BCF	-2-(3-bromopyridyl)	-isopropoxy
BCG	-2-(3-bromopyridyl)	$-CF_3$
BCH	-2-(3-bromopyridyl)	$-CH_2CF_3$
BCI	-2-(3-bromopyridyl)	$-OCF_3$
BCJ	-2-(3-bromopyridyl)	-Cl
BCK	-2-(3-bromopyridyl)	-Br
BCL	-2-(3-bromopyridyl)	-I
BCM	-2-(3-bromopyridyl)	-n-butyl
BCN	-2-(3-bromopyridyl)	-n-propyl
BCO	-2-(3-iodopyridyl)	-t-butyl
BCP	-2-(3-iodopyridyl)	-iso-butyl
BCQ	-2-(3-iodopyridyl)	-sec-butyl
BCR	-2-(3-iodopyridyl)	-cyclohexyl
BCS	-2-(3-iodopyridyl)	-t-butoxy

BCT	-2-(3-iodopyridyl)	-isopropoxy
BCU	-2-(3-iodopyridyl)	$-CF_3$
BCV	-2-(3-iodopyridyl)	$-CH_2CF_3$
BCW	-2-(3-iodopyridyl)	$-OCF_3$
BCX	-2-(3-iodopyridyl)	-Cl
BCY	-2-(3-iodopyridyl)	-Br
BCZ	-2-(3-iodopyridyl)	-I
BDA	-2-(3-iodopyridyl)	-n-butyl
BDB	-2-(3-iodopyridyl)	-n-propyl
BDC	-4-(5-chloropyrimidinyl)	-t-butyl
BDD	-4-(5-chloropyrimidinyl)	-iso-butyl
BDE	-4-(5-chloropyrimidinyl)	-sec-butyl
BDF	-4-(5-chloropyrimidinyl)	-cyclohexyl
BDG	-4-(5-chloropyrimidinyl)	-t-butoxy
BDH	-4-(5-chloropyrimidinyl)	-isopropoxy
BDI	-4-(5-chloropyrimidinyl)	$-CF_3$
BDJ	-4-(5-chloropyrimidinyl)	$-CH_2CF_3$
BDK	-4-(5-chloropyrimidinyl)	$-OCF_3$
BDL	-4-(5-chloropyrimidinyl)	-Cl
BDM	-4-(5-chloropyrimidinyl)	-Br
BDN	-4-(5-chloropyrimidinyl)	-I
BDO	-4-(5-chloropyrimidinyl)	-n-butyl
BDP	-4-(5-chloropyrimidinyl)	-n-propyl
BDQ	-4-(5-methylpyrimidinyl)	-t-butyl
BDR	-4-(5-methylpyrimidinyl)	-iso-butyl
BDS	-4-(5-methylpyrimidinyl)	-sec-butyl
BDT	-4-(5-methylpyrimidinyl)	-cyclohexyl
BDU	-4-(5-methylpyrimidinyl)	-t-butoxy
BDV	-4-(5-methylpyrimidinyl)	-isopropoxy

BDW	-4-(5-methylpyrimidinyl)	$-CF_3$
BDX	-4-(5-methylpyrimidinyl)	$-CH_2CF_3$
BDY	-4-(5-methylpyrimidinyl)	$-OCF_3$
BDZ	-4-(5-methylpyrimidinyl)	-Cl
BEA	-4-(5-methylpyrimidinyl)	-Br
BEB	-4-(5-methylpyrimidinyl)	-I
BEC	-4-(5-methylpyrimidinyl)	-n-butyl
BED	-4-(5-methylpyrimidinyl)	-n-propyl
BEE	-4-(5-fluoropyrimidinyl)	-t-butyl
BEF	-4-(5-fluoropyrimidinyl)	-iso-butyl
BEG	-4-(5-fluoropyrimidinyl)	-sec-butyl
BEH	-4-(5-fluoropyrimidinyl)	-cyclohexyl
BEI	-4-(5-fluoropyrimidinyl)	-t-butoxy
BEJ	-4-(5-fluoropyrimidinyl)	-isopropoxy
BEK	-4-(5-fluoropyrimidinyl)	$-CF_3$
BEL	-4-(5-fluoropyrimidinyl)	$-CH_2CF_3$
BEM	-4-(5-fluoropyrimidinyl)	$-OCF_3$
BEN	-4-(5-fluoropyrimidinyl)	-Cl
BEO	-4-(5-fluoropyrimidinyl)	-Br
BEP	-4-(5-fluoropyrimidinyl)	-I
BEQ	-4-(5-fluoropyrimidinyl)	-n-butyl
BER	-4-(5-fluoropyrimidinyl)	-n-propyl
BES	-2-(3-chloropyrazinyl)	-t-butyl
BET	-2-(3-chloropyrazinyl)	-iso-butyl
BEU	-2-(3-chloropyrazinyl)	-sec-butyl
BEV	-2-(3-chloropyrazinyl)	-cyclohexyl
BEW	-2-(3-chloropyrazinyl)	-t-butoxy
BEX	-2-(3-chloropyrazinyl)	-isopropoxy
BEY	-2-(3-chloropyrazinyl)	$-CF_3$

BEZ	-2-(3-chloropyrazinyl)	$-CH_2CF_3$
BFA	-2-(3-chloropyrazinyl)	$-OCF_3$
BFB	-2-(3-chloropyrazinyl)	-Cl
BFC	-2-(3-chloropyrazinyl)	-Br
BFD	-2-(3-chloropyrazinyl)	-I
BFE	-2-(3-chloropyrazinyl)	-n-butyl
BFF	-2-(3-chloropyrazinyl)	-n-propyl
BFG	-2-(3-methylpyrazinyl)	-t-butyl
BFH	-2-(3-methylpyrazinyl)	-iso-butyl
BFI	-2-(3-methylpyrazinyl)	-sec-butyl
BFJ	-2-(3-methylpyrazinyl)	-cyclohexyl
BFK	-2-(3-methylpyrazinyl)	-t-butoxy
BFL	-2-(3-methylpyrazinyl)	-isopropoxy
BFM	-2-(3-methylpyrazinyl)	$-CF_3$
BFN	-2-(3-methylpyrazinyl)	$-CH_2CF_3$
BFO	-2-(3-methylpyrazinyl)	$-OCF_3$
BFP	-2-(3-methylpyrazinyl)	-Cl
BFQ	-2-(3-methylpyrazinyl)	-Br
BFR	-2-(3-methylpyrazinyl)	-I
BFS	-2-(3-methylpyrazinyl)	-n-butyl
BFT	-2-(3-methylpyrazinyl)	-n-propyl
BFU	-2-(3-fluoropyrazinyl)	-t-butyl
BFV	-2-(3-fluoropyrazinyl)	-iso-butyl
BFW	-2-(3-fluoropyrazinyl)	-sec-butyl
BFX	-2-(3-fluoropyrazinyl)	-cyclohexyl
BFY	-2-(3-fluoropyrazinyl)	-t-butoxy
BFZ	-2-(3-fluoropyrazinyl)	-isopropoxy
BGA	-2-(3-fluoropyrazinyl)	$-CF_3$
BGB	-2-(3-fluoropyrazinyl)	$-CH_2CF_3$

BGC	-2-(3-fluoropyrazinyl)	$-OCF_3$
BGD	-2-(3-fluoropyrazinyl)	-Cl
BGE	-2-(3-fluoropyrazinyl)	-Br
BGF	-2-(3-fluoropyrazinyl)	-I
BGG	-2-(3-fluoropyrazinyl)	-n-butyl
BGH	-2-(3-fluoropyrazinyl)	-n-propyl
BGI	-3-(4-chloropyridazinyl)	-t-butyl
BGJ	-3-(4-chloropyridazinyl)	-iso-butyl
BGK	-3-(4-chloropyridazinyl)	-sec-butyl
BGL	-3-(4-chloropyridazinyl)	-cyclohexyl
BGM	-3-(4-chloropyridazinyl)	-t-butoxy
BGN	-3-(4-chloropyridazinyl)	-isopropoxy
BGO	-3-(4-chloropyridazinyl)	$-CF_3$
BGP	-3-(4-chloropyridazinyl)	$-CH_2CF_3$
BGQ	-3-(4-chloropyridazinyl)	$-OCF_3$
BGR	-3-(4-chloropyridazinyl)	-Cl
BGS	-3-(4-chloropyridazinyl)	-Br
BGT	-3-(4-chloropyridazinyl)	-I
BGU	-3-(4-chloropyridazinyl)	-n-butyl
BGV	-3-(4-chloropyridazinyl)	-n-propyl
BGW	-3-(4-methylpyridazinyl)	-t-butyl
BGX	-3-(4-methylpyridazinyl)	-iso-butyl
BGY	-3-(4-methylpyridazinyl)	-sec-butyl
BGZ	-3-(4-methylpyridazinyl)	-cyclohexyl
BHA	-3-(4-methylpyridazinyl)	-t-butoxy
BHB	-3-(4-methylpyridazinyl)	-isopropoxy
BHC	-3-(4-methylpyridazinyl)	$-CF_3$
BHD	-3-(4-methylpyridazinyl)	$-CH_2CF_3$
BHE	-3-(4-methylpyridazinyl)	$-OCF_3$

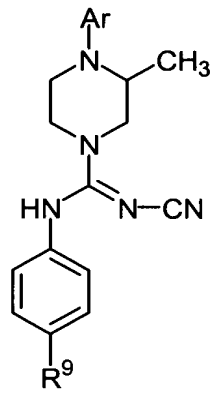
BHF	-3-(4-methylpyridazinyl)	-Cl
BHG	-3-(4-methylpyridazinyl)	-Br
BHH	-3-(4-methylpyridazinyl)	-I
BHI	-3-(4-methylpyridazinyl)	-n-butyl
BHJ	-3-(4-methylpyridazinyl)	-n-propyl
BHK	-3-(4-fluoropyridazinyl)	-t-butyl
BHL	-3-(4-fluoropyridazinyl)	-iso-butyl
BHM	-3-(4-fluoropyridazinyl)	-sec-butyl
BHN	-3-(4-fluoropyridazinyl)	-cyclohexyl
BHO	-3-(4-fluoropyridazinyl)	-t-butoxy
BHP	-3-(4-fluoropyridazinyl)	-isopropoxy
BHQ	-3-(4-fluoropyridazinyl)	$-CF_3$
BHR	-3-(4-fluoropyridazinyl)	$-CH_2CF_3$
BHS	-3-(4-fluoropyridazinyl)	$-OCF_3$
BHT	-3-(4-fluoropyridazinyl)	-Cl
BHU	-3-(4-fluoropyridazinyl)	-Br
BHV	-3-(4-fluoropyridazinyl)	-I
BHW	-3-(4-fluoropyridazinyl)	-n-butyl
BHX	-3-(4-fluoropyridazinyl)	-n-propyl
BHY	-5-(4-chlorothiadiazolyl)	-t-butyl
BHZ	-5-(4-chlorothiadiazolyl)	-iso-butyl
BIA	-5-(4-chlorothiadiazolyl)	-sec-butyl
BIB	-5-(4-chlorothiadiazolyl)	-cyclohexyl
BIC	-5-(4-chlorothiadiazolyl)	-t-butoxy
BID	-5-(4-chlorothiadiazolyl)	-isopropoxy
BIE	-5-(4-chlorothiadiazolyl)	$-CF_3$
BIF	-5-(4-chlorothiadiazolyl)	$-CH_2CF_3$
BIG	-5-(4-chlorothiadiazolyl)	$-OCF_3$
BIH	-5-(4-chlorothiadiazolyl)	-Cl

BII	-5-(4-chlorothiadiazolyl)	-Br
BIJ	-5-(4-chlorothiadiazolyl)	-I
BIK	-5-(4-chlorothiadiazolyl)	-n-butyl
BIL	-5-(4-chlorothiadiazolyl)	-n-propyl
BIM	-5-(4-methylthiadiazolyl)	-t-butyl
BIN	-5-(4-methylthiadiazolyl)	-iso-butyl
BIO	-5-(4-methylthiadiazolyl)	-sec-butyl
BIP	-5-(4-methylthiadiazolyl)	-cyclohexyl
BIQ	-5-(4-methylthiadiazolyl)	-t-butoxy
BIR	-5-(4-methylthiadiazolyl)	-isopropoxy
BIS	-5-(4-methylthiadiazolyl)	$-CF_3$
BIT	-5-(4-methylthiadiazolyl)	$-CH_2CF_3$
BIU	-5-(4-methylthiadiazolyl)	$-OCF_3$
BIV	-5-(4-methylthiadiazolyl)	-Cl
BIW	-5-(4-methylthiadiazolyl)	-Br
BIX	-5-(4-methylthiadiazolyl)	-I
BIY	-5-(4-methylthiadiazolyl)	-n-butyl
BIZ	-5-(4-methylthiadiazolyl)	-n-propyl
BJA	-5-(4-fluorothiadiazolyl)	-t-butyl
BJB	-5-(4-fluorothiadiazolyl)	-iso-butyl
BJC	-5-(4-fluorothiadiazolyl)	-sec-butyl
BJD	-5-(4-fluorothiadiazolyl)	-cyclohexyl
BJE	-5-(4-fluorothiadiazolyl)	-t-butoxy
BJF	-5-(4-fluorothiadiazolyl)	-isopropoxy
BJG	-5-(4-fluorothiadiazolyl)	$-CF_3$
BJH	-5-(4-fluorothiadiazolyl)	$-CH_2CF_3$
BJI	-5-(4-fluorothiadiazolyl)	$-OCF_3$
BJJ	-5-(4-fluorothiadiazolyl)	-Cl
BJK	-5-(4-fluorothiadiazolyl)	-Br

BJL	-5-(4-fluorothiadiazolyl)	-I
BJM	-5-(4-fluorothiadiazolyl)	-n-butyl
BJN	-5-(4-fluorothiadiazolyl)	-n-propyl

5

Table 4



IX

and pharmaceutically acceptable salts thereof, wherein:

Compound	Ar	R^9
BJO (a and b)	-2-(3-chloropyridyl)	-t-butyl
BJP (a and b)	-2-(3-chloropyridyl)	-iso-butyl
BJQ (a and b)	-2-(3-chloropyridyl)	-sec-butyl
BJR (a and b)	-2-(3-chloropyridyl)	-cyclohexyl
BJS (a and b)	-2-(3-chloropyridyl)	-t-butoxy
BJT (a and b)	-2-(3-chloropyridyl)	-isopropoxy
BJU (a and b)	-2-(3-chloropyridyl)	$-CF_3$
BJV (a and b)	-2-(3-chloropyridyl)	$-CH_2CF_3$
BJW (a and b)	-2-(3-chloropyridyl)	$-OCF_3$
BJX (a and b)	-2-(3-chloropyridyl)	-Cl
BJY (a and b)	-2-(3-chloropyridyl)	-Br
BJZ (a and b)	-2-(3-chloropyridyl)	-I
BKA (a and b)	-2-(3-chloropyridyl)	-n-butyl
BKB (a and b)	-2-(3-chloropyridyl)	-n-propyl
BKC (a and b)	-2-(3-fluoropyridyl)	-t-butyl

BKD (a and b)	-2-(3-fluoropyridyl)	-iso-butyl
BKE (a and b)	-2-(3-fluoropyridyl)	-sec-butyl
BKF (a and b)	-2-(3-fluoropyridyl)	-cyclohexyl
BKG (a and b)	-2-(3-fluoropyridyl)	-t-butoxy
BKH (a and b)	-2-(3-fluoropyridyl)	-isopropoxy
BKI (a and b)	-2-(3-fluoropyridyl)	$-CF_3$
BKJ (a and b)	-2-(3-fluoropyridyl)	$-CH_2CF_3$
BKK (a and b)	-2-(3-fluoropyridyl)	$-OCF_3$
BKL (a and b)	-2-(3-fluoropyridyl)	-Cl
BKM (a and b)	-2-(3-fluoropyridyl)	-Br
BKN (a and b)	-2-(3-fluoropyridyl)	-I
BKO (a and b)	-2-(3-fluoropyridyl)	-n-butyl
BKP (a and b)	-2-(3-fluoropyridyl)	-n-propyl
BKQ (a and b)	-2-(3-methylpyridyl)	-t-butyl
BKR (a and b)	-2-(3-methylpyridyl)	-iso-butyl
BKS (a and b)	-2-(3-methylpyridyl)	-sec-butyl
BKT (a and b)	-2-(3-methylpyridyl)	-cyclohexyl
BKU (a and b)	-2-(3-methylpyridyl)	-t-butoxy
BKV (a and b)	-2-(3-methylpyridyl)	-isopropoxy
BKW (a and b)	-2-(3-methylpyridyl)	$-CF_3$
BKX (a and b)	-2-(3-methylpyridyl)	$-CH_2CF_3$
BKY (a and b)	-2-(3-methylpyridyl)	$-OCF_3$
BKZ (a and b)	-2-(3-methylpyridyl)	-Cl
BLA (a and b)	-2-(3-methylpyridyl)	-Br
BLB (a and b)	-2-(3-methylpyridyl)	-I
BLC (a and b)	-2-(3-methylpyridyl)	-n-butyl
BLD (a and b)	-2-(3-methylpyridyl)	-n-propyl
BLE (a and b)	-2(3-CF_3-pyridyl)	-t-butyl
BLF (a and b)	-2-(3-CF_3-pyridyl)	-iso-butyl

BLG (a and b)	-2-(3-CF_3-pyridyl)	-sec-butyl
BLH (a and b)	-2-(3-CF_3-pyridyl)	-cyclohexyl
BLI (a and b)	-2-(3-CF_3-pyridyl)	-t-butoxy
BLJ (a and b)	-2-(3-CF_3-pyridyl)	-isopropoxy
BLK (a and b)	-2-(3-CF_3-pyridyl)	-CF_3
BLL (a and b)	-2-(3-CF_3-pyridyl)	-CH_2CF_3
BLM (a and b)	-2-(3-CF_3-pyridyl)	-OCF_3
BLN (a and b)	-2-(3-CF_3-pyridyl)	-Cl
BLO (a and b)	-2-(3-CF_3-pyridyl)	-Br
BLP (a and b)	-2-(3-CF_3-pyridyl)	-I
BLQ (a and b)	-2-(3-CF_3-pyridyl)	-n-butyl
BLR (a and b)	-2-(3-CF_3-pyridyl)	-n-propyl
BLS (a and b)	-2-(3-CHF_2-pyridyl)	-t-butyl
BLT (a and b)	-2-(3-CHF_2-pyridyl)	-iso-butyl
BLU (a and b)	-2-(3-CHF_2-pyridyl)	-sec-butyl
BLV (a and b)	-2-(3-CHF_2-pyridyl)	-cyclohexyl
BLW (a and b)	-2-(3-CHF_2-pyridyl)	-t-butoxy
BLX (a and b)	-2-(3-CHF_2-pyridyl)	-isopropoxy
BLY (a and b)	-2-(3-CHF_2-pyridyl)	-CF_3
BLZ (a and b)	-2-(3-CHF_2-pyridyl)	-CH_2CF_3
BMA (a and b)	-2-(3-CHF_2-pyridyl)	-OCF_3
BMB (a and b)	-2-(3-CHF_2-pyridyl)	-Cl
BMC (a and b)	-2-(3-CHF_2-pyridyl)	-Br
BMD (a and b)	-2-(3-CHF_2-pyridyl)	-I
BME (a and b)	-2-(3-CHF_2-pyridyl)	-n-butyl
BMF (a and b)	-2-(3-CHF_2-pyridyl)	-n-propyl
BMG (a and b)	-2-(3-hydroxypyridyl)	-t-butyl
BMH (a and b)	-2-(3-hydroxypyridyl)	-iso-butyl
BMI (a and b)	-2-(3-hydroxypyridyl)	-sec-butyl

BMJ (a and b)	-2-(3-hydroxypyridyl)	-cyclohexyl
BMK (a and b)	-2-(3-hydroxypyridyl)	-t-butoxy
BML (a and b)	-2-(3-hydroxypyridyl)	-isopropoxy
BMM (a and b)	-2-(3-hydroxypyridyl)	$-CF_3$
BMN (a and b)	-2-(3-hydroxypyridyl)	$-CH_2CF_3$
BMO (a and b)	-2-(3-hydroxypyridyl)	$-OCF_3$
BMP (a and b)	-2-(3-hydroxypyridyl)	-Cl
BMQ (a and b)	-2-(3-hydroxypyridyl)	-Br
BMR (a and b)	-2-(3-hydroxypyridyl)	-I
BMS (a and b)	-2-(3-hydroxypyridyl)	-n-butyl
BMT (a and b)	-2-(3-hydroxypyridyl)	-n-propyl
BMU (a and b)	-2-(3-nitropyridyl)	-t-butyl
BMV (a and b)	-2-(3-nitropyridyl)	-iso-butyl
BMW (a and b)	-2-(3-nitropyridyl)	-sec-butyl
BMX (a and b)	-2-(3-nitropyridyl)	-cyclohexyl
BMY (a and b)	-2-(3-nitropyridyl)	-t-butoxy
BMZ (a and b)	-2-(3-nitropyridyl)	-isopropoxy
BNA (a and b)	-2-(3-nitropyridyl)	$-CF_3$
BNB (a and b)	-2-(3-nitropyridyl)	$-CH_2CF_3$
BNC (a and b)	-2-(3-nitropyridyl)	$-OCF_3$
BND (a and b)	-2-(3-nitropyridyl)	-Cl
BNE (a and b)	-2-(3-nitropyridyl)	-Br
BNF (a and b)	-2-(3-nitropyridyl)	-I
BNG (a and b)	-2-(3-nitropyridyl)	-n-butyl
BNH (a and b)	-2-(3-nitropyridyl)	-n-propyl
BNI (a and b)	-2-(3-cyanopyridyl)	-t-butyl
BNJ (a and b)	-2-(3-cyanopyridyl)	-iso-butyl
BNK (a and b)	-2-(3-cyanopyridyl)	-sec-butyl
BNL (a and b)	-2-(3-cyanopyridyl)	-cyclohexyl

BNM (a and b)	-2-(3-cyanopyridyl)	-t-butoxy
BNN (a and b)	-2-(3-cyanopyridyl)	-isopropoxy
BNO (a and b)	-2-(3-cyanopyridyl)	$-CF_3$
BNP (a and b)	-2-(3-cyanopyridyl)	$-CH_2CF_3$
BNQ (a and b)	-2-(3-cyanopyridyl)	$-OCF_3$
BNR (a and b)	-2-(3-cyanopyridyl)	-Cl
BNS (a and b)	-2-(3-cyanopyridyl)	-Br
BNT (a and b)	-2-(3-cyanopyridyl)	-I
BNU (a and b)	-2-(3-cyanopyridyl)	-n-butyl
BNV (a and b)	-2-(3-cyanopyridyl)	-n-propyl
BNW (a and b)	-2-(3-bromopyridyl)	-t-butyl
BNX (a and b)	-2-(3-bromopyridyl)	-iso-butyl
BNY (a and b)	-2-(3-bromopyridyl)	-sec-butyl
BNZ (a and b)	-2-(3-bromopyridyl)	-cyclohexyl
BOA (a and b)	-2-(3-bromopyridyl)	-t-butoxy
BOB (a and b)	-2-(3-bromopyridyl)	-isopropoxy
BOC (a and b)	-2-(3-bromopyridyl)	$-CF_3$
BOD (a and b)	-2-(3-bromopyridyl)	$-CH_2CF_3$
BOE (a and b)	-2-(3-bromopyridyl)	$-OCF_3$
BOF (a and b)	-2-(3-bromopyridyl)	-Cl
BOG (a and b)	-2-(3-bromopyridyl)	-Br
BOH (a and b)	-2-(3-bromopyridyl)	-I
BOI (a and b)	-2-(3-bromopyridyl)	-n-butyl
BOJ (a and b)	-2-(3-bromopyridyl)	-n-propyl
BOK (a and b)	-2-(3-iodopyridyl)	-t-butyl
BOL (a and b)	-2-(3-iodopyridyl)	-iso-butyl
BOM (a and b)	-2-(3-iodopyridyl)	-sec-butyl
BON (a and b)	-2-(3-iodopyridyl)	-cyclohexyl
BOO (a and b)	-2-(3-iodopyridyl)	-t-butoxy

BOP (a and b)	-2-(3-iodopyridyl)	-isopropoxy
BOQ (a and b)	-2-(3-iodopyridyl)	$-CF_3$
BOR (a and b)	-2-(3-iodopyridyl)	$-CH_2CF_3$
BOS (a and b)	-2-(3-iodopyridyl)	$-OCF_3$
BOT (a and b)	-2-(3-iodopyridyl)	-Cl
BOU (a and b)	-2-(3-iodopyridyl)	-Br
BOV (a and b)	-2-(3-iodopyridyl)	-I
BOW (a and b)	-2-(3-iodopyridyl)	-n-butyl
BOX (a and b)	-2-(3-iodopyridyl)	-n-propyl
BOY (a and b)	-4-(5-chloropyrimidinyl)	-t-butyl
BOZ (a and b)	-4-(5-chloropyrimidinyl)	-iso-butyl
BPA (a and b)	-4-(5-chloropyrimidinyl)	-sec-butyl
BPB (a and b)	-4-(5-chloropyrimidinyl)	-cyclohexyl
BPC (a and b)	-4-(5-chloropyrimidinyl)	-t-butoxy
BPD (a and b)	-4-(5-chloropyrimidinyl)	-isopropoxy
BPE (a and b)	-4-(5-chloropyrimidinyl)	$-CF_3$
BPF (a and b)	-4-(5-chloropyrimidinyl)	$-CH_2CF_3$
BPG (a and b)	-4-(5-chloropyrimidinyl)	$-OCF_3$
BPH (a and b)	-4-(5-chloropyrimidinyl)	-Cl
BPI (a and b)	-4-(5-chloropyrimidinyl)	-Br
BPJ (a and b)	-4-(5-chloropyrimidinyl)	-I
BPK (a and b)	-4-(5-chloropyrimidinyl)	-n-butyl
BPL (a and b)	-4-(5-chloropyrimidinyl)	-n-propyl
BPM (a and b)	-4-(5-methylpyrimidinyl)	-t-butyl
BPN (a and b)	-4-(5-methylpyrimidinyl)	-iso-butyl
BPO (a and b)	-4-(5-methylpyrimidinyl)	-sec-butyl
BPP (a and b)	-4-(5-methylpyrimidinyl)	-cyclohexyl
BPQ (a and b)	-4-(5-methylpyrimidinyl)	-t-butoxy
BPR (a and b)	-4-(5-methylpyrimidinyl)	-isopropoxy

BPS (a and b)	-4-(5-methylpyrimidinyl)	$-CF_3$
BPT (a and b)	-4-(5-methylpyrimidinyl)	$-CH_2CF_3$
BPU (a and b)	-4-(5-methylpyrimidinyl)	$-OCF_3$
BPV (a and b)	-4-(5-methylpyrimidinyl)	-Cl
BPW (a and b)	-4-(5-methylpyrimidinyl)	-Br
BPX (a and b)	-4-(5-methylpyrimidinyl)	-I
BPY (a and b)	-4-(5-methylpyrimidinyl)	-n-butyl
BPZ (a and b)	-4-(5-methylpyrimidinyl)	-n-propyl
BQA (a and b)	-4-(5-fluoropyrimidinyl)	-t-butyl
BQB (a and b)	-4-(5-fluoropyrimidinyl)	-iso-butyl
BQC (a and b)	-4-(5-fluoropyrimidinyl)	-sec-butyl
BQD (a and b)	-4-(5-fluoropyrimidinyl)	-cyclohexyl
BQE (a and b)	-4-(5-fluoropyrimidinyl)	-t-butoxy
BQF (a and b)	-4-(5-fluoropyrimidinyl)	-isopropoxy
BQG (a and b)	-4-(5-fluoropyrimidinyl)	$-CF_3$
BQH (a and b)	-4-(5-fluoropyrimidinyl)	$-CH_2CF_3$
BQI (a and b)	-4-(5-fluoropyrimidinyl)	$-OCF_3$
BQJ (a and b)	-4-(5-fluoropyrimidinyl)	-Cl
BQK (a and b)	-4-(5-fluoropyrimidinyl)	-Br
BQL (a and b)	-4-(5-fluoropyrimidinyl)	-I
BQM (a and b)	-4-(5-fluoropyrimidinyl)	-n-butyl
BQN (a and b)	-4-(5-fluoropyrimidinyl)	-n-propyl
BQO (a and b)	-2-(3-chloropyrazinyl)	-t-butyl
BQP (a and b)	-2-(3-chloropyrazinyl)	-iso-butyl
BQQ (a and b)	-2-(3-chloropyrazinyl)	-sec-butyl
BQR (a and b)	-2-(3-chloropyrazinyl)	-cyclohexyl
BQS (a and b)	-2-(3-chloropyrazinyl)	-t-butoxy
BQT (a and b)	-2-(3-chloropyrazinyl)	-isopropoxy
BQU (a and b)	-2-(3-chloropyrazinyl)	$-CF_3$

BQV (a and b)	-2-(3-chloropyrazinyl)	$-CH_2CF_3$
BQW (a and b)	-2-(3-chloropyrazinyl)	$-OCF_3$
BQX (a and b)	-2-(3-chloropyrazinyl)	-Cl
BQY (a and b)	-2-(3-chloropyrazinyl)	-Br
BQZ (a and b)	-2-(3-chloropyrazinyl)	-I
BRA (a and b)	-2-(3-chloropyrazinyl)	-n-butyl
BRB (a and b)	-2-(3-chloropyrazinyl)	-n-propyl
BRC (a and b)	-2-(3-methylpyrazinyl)	-t-butyl
BRD (a and b)	-2-(3-methylpyrazinyl)	-iso-butyl
BRE (a and b)	-2-(3-methylpyrazinyl)	-sec-butyl
BRF (a and b)	-2-(3-methylpyrazinyl)	-cyclohexyl
BRG (a and b)	-2-(3-methylpyrazinyl)	-t-butoxy
BRH (a and b)	-2-(3-methylpyrazinyl)	-isopropoxy
BRI (a and b)	-2-(3-methylpyrazinyl)	$-CF_3$
BRJ (a and b)	-2-(3-methylpyrazinyl)	$-CH_2CF_3$
BRK (a and b)	-2-(3-methylpyrazinyl)	$-OCF_3$
BRL (a and b)	-2-(3-methylpyrazinyl)	-Cl
BRM (a and b)	-2-(3-methylpyrazinyl)	-Br
BRN (a and b)	-2-(3-methylpyrazinyl)	-I
BRO (a and b)	-2-(3-methylpyrazinyl)	-n-butyl
BRP (a and b)	-2-(3-methylpyrazinyl)	-n-propyl
BRQ (a and b)	-2-(3-fluoropyrazinyl)	-t-butyl
BRR (a and b)	-2-(3-fluoropyrazinyl)	-iso-butyl
BRS (a and b)	-2-(3-fluoropyrazinyl)	-sec-butyl
BRT (a and b)	-2-(3-fluoropyrazinyl)	-cyclohexyl
BRU (a and b)	-2-(3-fluoropyrazinyl)	-t-butoxy
BRV (a and b)	-2-(3-fluoropyrazinyl)	-isopropoxy
BRW (a and b)	-2-(3-fluoropyrazinyl)	$-CF_3$
BRX (a and b)	-2-(3-fluoropyrazinyl)	$-CH_2CF_3$

BRY (a and b)	-2-(3-fluoropyrazinyl)	$-OCF_3$
BRZ (a and b)	-2-(3-fluoropyrazinyl)	-Cl
BSA (a and b)	-2-(3-fluoropyrazinyl)	-Br
BSB (a and b)	-2-(3-fluoropyrazinyl)	-I
BSC (a and b)	-2-(3-fluoropyrazinyl)	-n-butyl
BSD (a and b)	-2-(3-fluoropyrazinyl)	-n-propyl
BSE (a and b)	-3-(4-chloropyridazinyl)	-t-butyl
BSF (a and b)	-3-(4-chloropyridazinyl)	-iso-butyl
BSG (a and b)	-3-(4-chloropyridazinyl)	-sec-butyl
BSH (a and b)	-3-(4-chloropyridazinyl)	-cyclohexyl
BSI (a and b)	-3-(4-chloropyridazinyl)	-t-butoxy
BSJ (a and b)	-3-(4-chloropyridazinyl)	-isopropoxy
BSK (a and b)	-3-(4-chloropyridazinyl)	$-CF_3$
BSL (a and b)	-3-(4-chloropyridazinyl)	$-CH_2CF_3$
BSM (a and b)	-3-(4-chloropyridazinyl)	$-OCF_3$
BSN (a and b)	-3-(4-chloropyridazinyl)	-Cl
BSO (a and b)	-3-(4-chloropyridazinyl)	-Br
BSP (a and b)	-3-(4-chloropyridazinyl)	-I
BSQ (a and b)	-3-(4-chloropyridazinyl)	-n-butyl
BSR (a and b)	-3-(4-chloropyridazinyl)	-n-propyl
BSS (a and b)	-3-(4-methylpyridazinyl)	-t-butyl
BST (a and b)	-3-(4-methylpyridazinyl)	-iso-butyl
BSU (a and b)	-3-(4-methylpyridazinyl)	-sec-butyl
BSV (a and b)	-3-(4-methylpyridazinyl)	-cyclohexyl
BSW (a and b)	-3-(4-methylpyridazinyl)	-t-butoxy
BSX (a and b)	-3-(4-methylpyridazinyl)	-isopropoxy
BSY (a and b)	-3-(4-methylpyridazinyl)	$-CF_3$
BSZ (a and b)	-3-(4-methylpyridazinyl)	$-CH_2CF_3$
BTA (a and b)	-3-(4-methylpyridazinyl)	$-OCF_3$

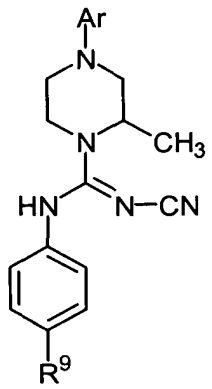
BTB (a and b)	-3-(4-methylpyridazinyl)	-Cl
BTC (a and b)	-3-(4-methylpyridazinyl)	-Br
BTD (a and b)	-3-(4-methylpyridazinyl)	-I
BTE (a and b)	-3-(4-methylpyridazinyl)	-n-butyl
BTF (a and b)	-3-(4-methylpyridazinyl)	-n-propyl
BTG (a and b)	-3-(4-fluoropyridazinyl)	-t-butyl
BTH (a and b)	-3-(4-fluoropyridazinyl)	-iso-butyl
BTI (a and b)	-3-(4-fluoropyridazinyl)	-sec-butyl
BTJ (a and b)	-3-(4-fluoropyridazinyl)	-cyclohexyl
BTK (a and b)	-3-(4-fluoropyridazinyl)	-t-butoxy
BTL (a and b)	-3-(4-fluoropyridazinyl)	-isopropoxy
BTM (a and b)	-3-(4-fluoropyridazinyl)	$-CF_3$
BTN (a and b)	-3-(4-fluoropyridazinyl)	$-CH_2CF_3$
BTO (a and b)	-3-(4-fluoropyridazinyl)	$-OCF_3$
BTP (a and b)	-3-(4-fluoropyridazinyl)	-Cl
BTQ (a and b)	-3-(4-fluoropyridazinyl)	-Br
BTR (a and b)	-3-(4-fluoropyridazinyl)	-I
BTS (a and b)	-3-(4-fluoropyridazinyl)	-n-butyl
BTT (a and b)	-3-(4-fluoropyridazinyl)	-n-propyl
BTU (a and b)	-5-(4-chlorothiadiazolyl)	-t-butyl
BTV (a and b)	-5-(4-chlorothiadiazolyl)	-iso-butyl
BTW (a and b)	-5-(4-chlorothiadiazolyl)	-sec-butyl
BTX (a and b)	-5-(4-chlorothiadiazolyl)	-cyclohexyl
BTY (a and b)	-5-(4-chlorothiadiazolyl)	-t-butoxy
BTZ (a and b)	-5-(4-chlorothiadiazolyl)	-isopropoxy
BUA (a and b)	-5-(4-chlorothiadiazolyl)	$-CF_3$
BUB (a and b)	-5-(4-chlorothiadiazolyl)	$-CH_2CF_3$
BUC (a and b)	-5-(4-chlorothiadiazolyl)	$-OCF_3$
BUD (a and b)	-5-(4-chlorothiadiazolyl)	-Cl

BUE (a and b)	-5-(4-chlorothiadiazolyl)	-Br
BUF (a and b)	-5-(4-chlorothiadiazolyl)	-I
BUG (a and b)	-5-(4-chlorothiadiazolyl)	-n-butyl
BUH (a and b)	-5-(4-chlorothiadiazolyl)	-n-propyl
BUI (a and b)	-5-(4-methylthiadiazolyl)	-t-butyl
BUJ (a and b)	-5-(4-methylthiadiazolyl)	-iso-butyl
BUK (a and b)	-5-(4-methylthiadiazolyl)	-sec-butyl
BUL (a and b)	-5-(4-methylthiadiazolyl)	-cyclohexyl
BUM (a and b)	-5-(4-methylthiadiazolyl)	-t-butoxy
BUN (a and b)	-5-(4-methylthiadiazolyl)	-isopropoxy
BUO (a and b)	-5-(4-methylthiadiazolyl)	$-CF_3$
BUP (a and b)	-5-(4-methylthiadiazolyl)	$-CH_2CF_3$
BUQ (a and b)	-5-(4-methylthiadiazolyl)	$-OCF_3$
BUR (a and b)	-5-(4-methylthiadiazolyl)	-Cl
BUS (a and b)	-5-(4-methylthiadiazolyl)	-Br
BUT (a and b)	-5-(4-methylthiadiazolyl)	-I
BUU (a and b)	-5-(4-methylthiadiazolyl)	-n-butyl
BUV (a and b)	-5-(4-methylthiadiazolyl)	-n-propyl
BUW (a and b)	-5-(4-fluorothiadiazolyl)	-t-butyl
BUX (a and b)	-5-(4-fluorothiadiazolyl)	-iso-butyl
BUY (a and b)	-5-(4-fluorothiadiazolyl)	-sec-butyl
BUZ (a and b)	-5-(4-fluorothiadiazolyl)	-cyclohexyl
BVA (a and b)	-5-(4-fluorothiadiazolyl)	-t-butoxy
BVB (a and b)	-5-(4-fluorothiadiazolyl)	-isopropoxy
BVC (a and b)	-5-(4-fluorothiadiazolyl)	$-CF_3$
BVD (a and b)	-5-(4-fluorothiadiazolyl)	$-CH_2CF_3$
BVE (a and b)	-5-(4-fluorothiadiazolyl)	$-OCF_3$
BVF (a and b)	-5-(4-fluorothiadiazolyl)	-Cl
BVG (a and b)	-5-(4-fluorothiadiazolyl)	-Br

BVH (a and b)	-5-(4-fluorothiadiazolyl)	-I
BVI (a and b)	-5-(4-fluorothiadiazolyl)	-n-butyl
BVJ (a and b)	-5-(4-fluorothiadiazolyl)	-n-propyl

wherein "a" means that the carbon atom of the piperazino group to which the methyl group is attached is in the R configuration and "b" means that the carbon of the piperazino group to which the methyl group is attached is in the S configuration

Table 5



X

and pharmaceutically acceptable salts thereof, wherein:

Compound	Ar	R^9
BVK (a and b)	-2-(3-chloropyridyl)	-t-butyl
BVL (a and b)	-2-(3-chloropyridyl)	-iso-butyl
BVM (a and b)	-2-(3-chloropyridyl)	-sec-butyl
BVN (a and b)	-2-(3-chloropyridyl)	-cyclohexyl
BVO (a and b)	-2-(3-chloropyridyl)	-t-butoxy
BVP (a and b)	-2-(3-chloropyridyl)	-isopropoxy
BVQ (a and b)	-2-(3-chloropyridyl)	$-CF_3$
BVR (a and b)	-2-(3-chloropyridyl)	$-CH_2CF_3$
BVS (a and b)	-2-(3-chloropyridyl)	$-OCF_3$
BVT (a and b)	-2-(3-chloropyridyl)	-Cl
BVU (a and b)	-2-(3-chloropyridyl)	-Br
BVV (a and b)	-2-(3-chloropyridyl)	-I
BVW (a and b)	-2-(3-chloropyridyl)	-n-butyl
BVX (a and b)	-2-(3-chloropyridyl)	-n-propyl
BVY (a and b)	-2-(3-fluoropyridyl)	-t-butyl
BVZ (a and b)	-2-(3-fluoropyridyl)	-iso-butyl

BWA (a and b)	-2-(3-fluoropyridyl)	-sec-butyl
BWB (a and b)	-2-(3-fluoropyridyl)	-cyclohexyl
BWC (a and b)	-2-(3-fluoropyridyl)	-t-butoxy
BWD (a and b)	-2-(3-fluoropyridyl)	-isopropoxy
BWE (a and b)	-2-(3-fluoropyridyl)	$-CF_3$
BWF (a and b)	-2-(3-fluoropyridyl)	$-CH_2CF_3$
BWG (a and b)	-2-(3-fluoropyridyl)	$-OCF_3$
BWH (a and b)	-2-(3-fluoropyridyl)	-Cl
BWI (a and b)	-2-(3-fluoropyridyl)	-Br
BWJ (a and b)	-2-(3-fluoropyridyl)	-I
BWK (a and b)	-2-(3-fluoropyridyl)	-n-butyl
BWL (a and b)	-2-(3-fluoropyridyl)	-n-propyl
BWM (a and b)	-2-(3-methylpyridyl)	-t-butyl
BWN (a and b)	-2-(3-methylpyridyl)	-iso-butyl
BWO (a and b)	-2-(3-methylpyridyl)	-sec-butyl
BWP (a and b)	-2-(3-methylpyridyl)	-cyclohexyl
BWQ (a and b)	-2-(3-methylpyridyl)	-t-butoxy
BWR (a and b)	-2-(3-methylpyridyl)	-isopropoxy
BWS (a and b)	-2-(3-methylpyridyl)	$-CF_3$
BWT (a and b)	-2-(3-methylpyridyl)	$-CH_2CF_3$
BWU (a and b)	-2-(3-methylpyridyl)	$-OCF_3$
BWV (a and b)	-2-(3-methylpyridyl)	-Cl
BWW (a and b)	-2-(3-methylpyridyl)	-Br
BWX (a and b)	-2-(3-methylpyridyl)	-I
BWY (a and b)	-2-(3-methylpyridyl)	-n-butyl
BWZ (a and b)	-2-(3-methylpyridyl)	-n-propyl
BXA (a and b)	-2-(3-CF_3-pyridyl)	-t-butyl
BXB (a and b)	-2-(3-CF_3-pyridyl)	-iso-butyl
BXC (a and b)	-2-(3-CF_3-pyridyl)	-sec-butyl

BXD (a and b)	-2-(3-CF_3-pyridyl)	-cyclohexyl
BXE (a and b)	-2-(3-CF_3-pyridyl)	-t-butoxy
BXF (a and b)	-2-(3-CF_3-pyridyl)	-isopropoxy
BXG (a and b)	-2-(3-CF_3-pyridyl)	-CF_3
BXH (a and b)	-2-(3-CF_3-pyridyl)	-CH_2CF_3
BXI (a and b)	-2-(3-CF_3-pyridyl)	-OCF_3
BXJ (a and b)	-2-(3-CF_3-pyridyl)	-Cl
BXK (a and b)	-2-(3-CF_3-pyridyl)	-Br
BXL (a and b)	-2-(3-CF_3-pyridyl)	-I
BXM (a and b)	-2-(3-CF_3-pyridyl)	-n-butyl
BXN (a and b)	-2-(3-CF_3-pyridyl)	-n-propyl
BXO (a and b)	-2-(3-CHF_2-pyridyl)	-t-butyl
BXP (a and b)	-2-(3-CHF_2-pyridyl)	-iso-butyl
BXQ (a and b)	-2-(3-CHF_2-pyridyl)	-sec-butyl
BXR (a and b)	-2-(3-CHF_2-pyridyl)	-cyclohexyl
BXS (a and b)	-2-(3-CHF_2-pyridyl)	-t-butoxy
BXT (a and b)	-2-(3-CHF_2-pyridyl)	-isopropoxy
BXU (a and b)	-2-(3-CHF_2-pyridyl)	-CF_3
BXV (a and b)	-2-(3-CHF_2-pyridyl)	-CH_2CF_3
BXW (a and b)	-2-(3-CHF_2-pyridyl)	-OCF_3
BXX (a and b)	-2-(3-CHF_2-pyridyl)	-Cl
BXY (a and b)	-2-(3-CHF_2-pyridyl)	-Br
BXZ (a and b)	-2-(3-CHF_2-pyridyl)	-I
BYA (a and b)	-2-(3-CHF_2-pyridyl)	-n-butyl
BYB (a and b)	-2-(3-CHF_2-pyridyl)	-n-propyl
BYC (a and b)	-2-(3-hydroxypyridyl)	-t-butyl
BYD (a and b)	-2-(3-hydroxypyridyl)	-iso-butyl
BYE (a and b)	-2-(3-hydroxypyridyl)	-sec-butyl
BYF (a and b)	-2-(3-hydroxypyridyl)	-cyclohexyl

BYG (a and b)	-2-(3-hydroxypyridyl)	-t-butoxy
BYH (a and b)	-2-(3-hydroxypyridyl)	-isopropoxy
BYI (a and b)	-2-(3-hydroxypyridyl)	$-CF_3$
BYJ (a and b)	-2-(3-hydroxypyridyl)	$-CH_2CF_3$
BYK (a and b)	-2-(3-hydroxypyridyl)	$-OCF_3$
BYL (a and b)	-2-(3-hydroxypyridyl)	-Cl
BYM (a and b)	-2-(3-hydroxypyridyl)	-Br
BYN (a and b)	-2-(3-hydroxypyridyl)	-I
BYO (a and b)	-2-(3-hydroxypyridyl)	-n-butyl
BYP (a and b)	-2-(3-hydroxypyridyl)	-n-propyl
BYQ (a and b)	-2-(3-nitropyridyl)	-t-butyl
BYR (a and b)	-2-(3-nitropyridyl)	-iso-butyl
BYS (a and b)	-2-(3-nitropyridyl)	-sec-butyl
BYT (a and b)	-2-(3-nitropyridyl)	-cyclohexyl
BYU (a and b)	-2-(3-nitropyridyl)	-t-butoxy
BYV (a and b)	-2-(3-nitropyridyl)	-isopropoxy
BYW (a and b)	-2-(3-nitropyridyl)	$-CF_3$
BYX (a and b)	-2-(3-nitropyridyl)	$-CH_2CF_3$
BYY (a and b)	-2-(3-nitropyridyl)	$-OCF_3$
BYZ (a and b)	-2-(3-nitropyridyl)	-Cl
BZA (a and b)	-2-(3-nitropyridyl)	-Br
BZB (a and b)	-2-(3-nitropyridyl)	-I
BZC (a and b)	-2-(3-nitropyridyl)	-n-butyl
BZD (a and b)	-2-(3-nitropyridyl)	-n-propyl
BZE (a and b)	-2-(3-cyanopyridyl)	-t-butyl
BZF (a and b)	-2-(3-cyanopyridyl)	-iso-butyl
BZG (a and b)	-2-(3-cyanopyridyl)	-sec-butyl
BZH (a and b)	-2-(3-cyanopyridyl)	-cyclohexyl
BZI (a and b)	-2-(3-cyanopyridyl)	-t-butoxy

BZJ (a and b)	-2-(3-cyanopyridyl)	-isopropoxy
BZK (a and b)	-2-(3-cyanopyridyl)	$-CF_3$
BZL (a and b)	-2-(3-cyanopyridyl)	$-CH_2CF_3$
BZM (a and b)	-2-(3-cyanopyridyl)	$-OCF_3$
BZN (a and b)	-2-(3-cyanopyridyl)	-Cl
BZO (a and b)	-2-(3-cyanopyridyl)	-Br
BZP (a and b)	-2-(3-cyanopyridyl)	-I
BZQ (a and b)	-2-(3-cyanopyridyl)	-n-butyl
BZR (a and b)	-2-(3-cyanopyridyl)	-n-propyl
BZS (a and b)	-2-(3-bromopyridyl)	-t-butyl
BZT (a and b)	-2-(3-bromopyridyl)	-iso-butyl
BZU (a and b)	-2-(3-bromopyridyl)	-sec-butyl
BZV (a and b)	-2-(3-bromopyridyl)	-cyclohexyl
BZW (a and b)	-2-(3-bromopyridyl)	-t-butoxy
BZX (a and b)	-2-(3-bromopyridyl)	-isopropoxy
BZY (a and b)	-2-(3-bromopyridyl)	$-CF_3$
BZZ (a and b)	-2-(3-bromopyridyl)	$-CH_2CF_3$
CAA (a and b)	-2-(3-bromopyridyl)	$-OCF_3$
CAB (a and b)	-2-(3-bromopyridyl)	-Cl
CAC (a and b)	-2-(3-bromopyridyl)	-Br
CAD (a and b)	-2-(3-bromopyridyl)	-I
CAE (a and b)	-2-(3-bromopyridyl)	-n-butyl
CAF (a and b)	-2-(3-bromopyridyl)	-n-propyl
CAG (a and b)	-2-(3-iodopyridyl)	-t-butyl
CAH (a and b)	-2-(3-iodopyridyl)	-iso-butyl
CAI (a and b)	-2-(3-iodopyridyl)	-sec-butyl
CAJ (a and b)	-2-(3-iodopyridyl)	-cyclohexyl
CAK (a and b)	-2-(3-iodopyridyl)	-t-butoxy
CAL (a and b)	-2-(3-iodopyridyl)	-isopropoxy

CAM (a and b)	-2-(3-iodopyridyl)	$-CF_3$
CAN (a and b)	-2-(3-iodopyridyl)	$-CH_2CF_3$
CAO (a and b)	-2-(3-iodopyridyl)	$-OCF_3$
CAP (a and b)	-2-(3-iodopyridyl)	-Cl
CAQ (a and b)	-2-(3-iodopyridyl)	-Br
CAR (a and b)	-2-(3-iodopyridyl)	-I
CAS (a and b)	-2-(3-iodopyridyl)	-n-butyl
CAT (a and b)	-2-(3-iodopyridyl)	-n-propyl
CAU (a and b)	-4-(5-chloropyrimidinyl)	-t-butyl
CAV (a and b)	-4-(5-chloropyrimidinyl)	-iso-butyl
CAW (a and b)	-4-(5-chloropyrimidinyl)	-sec-butyl
CAX (a and b)	-4-(5-chloropyrimidinyl)	-cyclohexyl
CAY (a and b)	-4-(5-chloropyrimidinyl)	-t-butoxy
CAZ (a and b)	-4-(5-chloropyrimidinyl)	-isopropoxy
CBA (a and b)	-4-(5-chloropyrimidinyl)	$-CF_3$
CBB (a and b)	-4-(5-chloropyrimidinyl)	$-CH_2CF_3$
CBC (a and b)	-4-(5-chloropyrimidinyl)	$-OCF_3$
CBD (a and b)	-4-(5-chloropyrimidinyl)	-Cl
CBE (a and b)	-4-(5-chloropyrimidinyl)	-Br
CBF (a and b)	-4-(5-chloropyrimidinyl)	-I
CBG (a and b)	-4-(5-chloropyrimidinyl)	-n-butyl
CBH (a and b)	-4-(5-chloropyrimidinyl)	-n-propyl
CBI (a and b)	-4-(5-methylpyrimidinyl)	-t-butyl
CBJ (a and b)	-4-(5-methylpyrimidinyl)	-iso-butyl
CBK (a and b)	-4-(5-methylpyrimidinyl)	-sec-butyl
CBL (a and b)	-4-(5-methylpyrimidinyl)	-cyclohexyl
CBM (a and b)	-4-(5-methylpyrimidinyl)	-t-butoxy
CBN (a and b)	-4-(5-methylpyrimidinyl)	-isopropoxy
CBO (a and b)	-4-(5-methylpyrimidinyl)	$-CF_3$

CBP (a and b)	-4-(5-methylpyrimidinyl)	$-CH_2CF_3$
CBQ (a and b)	-4-(5-methylpyrimidinyl)	$-OCF_3$
CBR (a and b)	-4-(5-methylpyrimidinyl)	-Cl
CBS (a and b)	-4-(5-methylpyrimidinyl)	-Br
CBT (a and b)	-4-(5-methylpyrimidinyl)	-I
CBU (a and b)	-4-(5-methylpyrimidinyl)	-n-butyl
CBV (a and b)	-4-(5-methylpyrimidinyl)	-n-propyl
CBW (a and b)	-4-(5-fluoropyrimidinyl)	-t-butyl
CBX (a and b)	-4-(5-fluoropyrimidinyl)	-iso-butyl
CBY (a and b)	-4-(5-fluoropyrimidinyl)	-sec-butyl
CBZ (a and b)	-4-(5-fluoropyrimidinyl)	-cyclohexyl
CCA (a and b)	-4-(5-fluoropyrimidinyl)	-t-butoxy
CCB (a and b)	-4-(5-fluoropyrimidinyl)	-isopropoxy
CCC (a and b)	-4-(5-fluoropyrimidinyl)	$-CF_3$
CCD (a and b)	-4-(5-fluoropyrimidinyl)	$-CH_2CF_3$
CCE (a and b)	-4-(5-fluoropyrimidinyl)	$-OCF_3$
CCF (a and b)	-4-(5-fluoropyrimidinyl)	-Cl
CCG (a and b)	-4-(5-fluoropyrimidinyl)	-Br
CCH (a and b)	-4-(5-fluoropyrimidinyl)	-I
CCI (a and b)	-4-(5-fluoropyrimidinyl)	-n-butyl
CCJ (a and b)	-4-(5-fluoropyrimidinyl)	-n-propyl
CCK (a and b)	-2-(3-chloropyrazinyl)	-t-butyl
CCL (a and b)	-2-(3-chloropyrazinyl)	-iso-butyl
CCM (a and b)	-2-(3-chloropyrazinyl)	-sec-butyl
CCN (a and b)	-2-(3-chloropyrazinyl)	-cyclohexyl
CCO (a and b)	-2-(3-chloropyrazinyl)	-t-butoxy
CCP (a and b)	-2-(3-chloropyrazinyl)	-isopropoxy
CCQ (a and b)	-2-(3-chloropyrazinyl)	$-CF_3$
CCR (a and b)	-2-(3-chloropyrazinyl)	$-CH_2CF_3$

CCS (a and b)	-2-(3-chloropyrazinyl)	$-OCF_3$
CCT (a and b)	-2-(3-chloropyrazinyl)	-Cl
CCU (a and b)	-2-(3-chloropyrazinyl)	-Br
CCV (a and b)	-2-(3-chloropyrazinyl)	-I
CCW (a and b)	-2-(3-chloropyrazinyl)	-n-butyl
CCX (a and b)	-2-(3-chloropyrazinyl)	-n-propyl
CCY (a and b)	-2-(3-methylpyrazinyl)	-t-butyl
CCZ (a and b)	-2-(3-methylpyrazinyl)	-iso-butyl
CDA (a and b)	-2-(3-methylpyrazinyl)	-sec-butyl
CDB (a and b)	-2-(3-methylpyrazinyl)	-cyclohexyl
CDC (a and b)	-2-(3-methylpyrazinyl)	-t-butoxy
CDD (a and b)	-2-(3-methylpyrazinyl)	-isopropoxy
CDE (a and b)	-2-(3-methylpyrazinyl)	$-CF_3$
CDF (a and b)	-2-(3-methylpyrazinyl)	$-CH_2CF_3$
CDG (a and b)	-2-(3-methylpyrazinyl)	$-OCF_3$
CDH (a and b)	-2-(3-methylpyrazinyl)	-Cl
CDI (a and b)	-2-(3-methylpyrazinyl)	-Br
CDJ (a and b)	-2-(3-methylpyrazinyl)	-I
CDK (a and b)	-2-(3-methylpyrazinyl)	-n-butyl
CDL (a and b)	-2-(3-methylpyrazinyl)	-n-propyl
CDM (a and b)	-2-(3-fluoropyrazinyl)	-t-butyl
CDN (a and b)	-2-(3-fluoropyrazinyl)	-iso-butyl
CDO (a and b)	-2-(3-fluoropyrazinyl)	-sec-butyl
CDP (a and b)	-2-(3-fluoropyrazinyl)	-cyclohexyl
CDQ (a and b)	-2-(3-fluoropyrazinyl)	-t-butoxy
CDR (a and b)	-2-(3-fluoropyrazinyl)	-isopropoxy
CDS (a and b)	-2-(3-fluoropyrazinyl)	$-CF_3$
CDT (a and b)	-2-(3-fluoropyrazinyl)	$-CH_2CF_3$
CDU	-2-(3-fluoropyrazinyl)	$-OCF_3$

CDV (a and b)	-2-(3-fluoropyrazinyl)	-Cl
CDW (a and b)	-2-(3-fluoropyrazinyl)	-Br
CDX (a and b)	-2-(3-fluoropyrazinyl)	-I
CDY (a and b)	-2-(3-fluoropyrazinyl)	-n-butyl
CDZ (a and b)	-2-(3-fluoropyrazinyl)	-n-propyl
CEA (a and b)	-3-(4-chloropyridazinyl)	-t-butyl
CEB (a and b)	-3-(4-chloropyridazinyl)	-iso-butyl
CEC (a and b)	-3-(4-chloropyridazinyl)	-sec-butyl
CED (a and b)	-3-(4-chloropyridazinyl)	-cyclohexyl
CEE (a and b)	-3-(4-chloropyridazinyl)	-t-butoxy
CEF (a and b)	-3-(4-chloropyridazinyl)	-isopropoxy
CEG (a and b)	-3-(4-chloropyridazinyl)	$-CF_3$
CEH (a and b)	-3-(4-chloropyridazinyl)	$-CH_2CF_3$
CEI (a and b)	-3-(4-chloropyridazinyl)	$-OCF_3$
CEJ (a and b)	-3-(4-chloropyridazinyl)	-Cl
CEK (a and b)	-3-(4-chloropyridazinyl)	-Br
CEL (a and b)	-3-(4-chloropyridazinyl)	-I
CEM (a and b)	-3-(4-chloropyridazinyl)	-n-butyl
CEN (a and b)	-3-(4-chloropyridazinyl)	-n-propyl
CEO (a and b)	-3-(4-methylpyridazinyl)	-t-butyl
CEP (a and b)	-3-(4-methylpyridazinyl)	-iso-butyl
CEQ (a and b)	-3-(4-methylpyridazinyl)	-sec-butyl
CER (a and b)	-3-(4-methylpyridazinyl)	-cyclohexyl
CES (a and b)	-3-(4-methylpyridazinyl)	-t-butoxy
CET (a and b)	-3-(4-methylpyridazinyl)	-isopropoxy
CEU (a and b)	-3-(4-methylpyridazinyl)	$-CF_3$
CEV (a and b)	-3-(4-methylpyridazinyl)	$-CH_2CF_3$
CEW (a and b)	-3-(4-methylpyridazinyl)	$-OCF_3$
CEX (a and b)	-3-(4-methylpyridazinyl)	-Cl

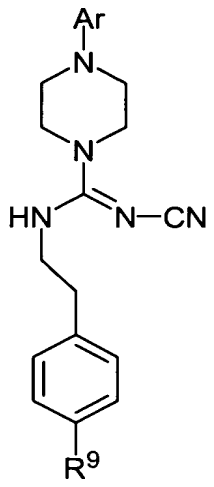
CEY (a and b)	-3-(4-methylpyridazinyl)	-Br
CEZ (a and b)	-3-(4-methylpyridazinyl)	-I
CFA (a and b)	-3-(4-methylpyridazinyl)	-n-butyl
CFB (a and b)	-3-(4-methylpyridazinyl)	-n-propyl
CFC (a and b)	-3-(4-fluoropyridazinyl)	-t-butyl
CFD (a and b)	-3-(4-fluoropyridazinyl)	-iso-butyl
CFE (a and b)	-3-(4-fluoropyridazinyl)	-sec-butyl
CFF (a and b)	-3-(4-fluoropyridazinyl)	-cyclohexyl
CFG (a and b)	-3-(4-fluoropyridazinyl)	-t-butoxy
CFH (a and b)	-3-(4-fluoropyridazinyl)	-isopropoxy
CFI (a and b)	-3-(4-fluoropyridazinyl)	$-CF_3$
CFJ (a and b)	-3-(4-fluoropyridazinyl)	$-CH_2CF_3$
CFK (a and b)	-3-(4-fluoropyridazinyl)	$-OCF_3$
CFL (a and b)	-3-(4-fluoropyridazinyl)	-Cl
CFM (a and b)	-3-(4-fluoropyridazinyl)	-Br
CFN (a and b)	-3-(4-fluoropyridazinyl)	-I
CFO (a and b)	-3-(4-fluoropyridazinyl)	-n-butyl
CFP (a and b)	-3-(4-fluoropyridazinyl)	-n-propyl
CFQ (a and b)	-5-(4-chlorothiadiazolyl)	-t-butyl
CFR (a and b)	-5-(4-chlorothiadiazolyl)	-iso-butyl
CFS (a and b)	-5-(4-chlorothiadiazolyl)	-sec-butyl
CFT (a and b)	-5-(4-chlorothiadiazolyl)	-cyclohexyl
CFU (a and b)	-5-(4-chlorothiadiazolyl)	-t-butoxy
CFV (a and b)	-5-(4-chlorothiadiazolyl)	-isopropoxy
CFW (a and b)	-5-(4-chlorothiadiazolyl)	$-CF_3$
CFX (a and b)	-5-(4-chlorothiadiazolyl)	$-CH_2CF_3$
CFY (a and b)	-5-(4-chlorothiadiazolyl)	$-OCF_3$
CFZ (a and b)	-5-(4-chlorothiadiazolyl)	-Cl
CGA (a and b)	-5-(4-chlorothiadiazolyl)	-Br

CGB (a and b)	-5-(4-chlorothiadiazolyl)	-I
CGC (a and b)	-5-(4-chlorothiadiazolyl)	-n-butyl
CGD (a and b)	-5-(4-chlorothiadiazolyl)	-n-propyl
CGE (a and b)	-5-(4-methylthiadiazolyl)	-t-butyl
CGF (a and b)	-5-(4-methylthiadiazolyl)	-iso-butyl
CGG (a and b)	-5-(4-methylthiadiazolyl)	-sec-butyl
CGH (a and b)	-5-(4-methylthiadiazolyl)	-cyclohexyl
CGI (a and b)	-5-(4-methylthiadiazolyl)	-t-butoxy
CGJ (a and b)	-5-(4-methylthiadiazolyl)	-isopropoxy
CGK (a and b)	-5-(4-methylthiadiazolyl)	$-CF_3$
CGL (a and b)	-5-(4-methylthiadiazolyl)	$-CH_2CF_3$
CGM (a and b)	-5-(4-methylthiadiazolyl)	$-OCF_3$
CGN (a and b)	-5-(4-methylthiadiazolyl)	-Cl
CGO (a and b)	-5-(4-methylthiadiazolyl)	-Br
CGP (a and b)	-5-(4-methylthiadiazolyl)	-I
CGQ (a and b)	-5-(4-methylthiadiazolyl)	-n-butyl
CGR (a and b)	-5-(4-methylthiadiazolyl)	-n-propyl
CGS (a and b)	-5-(4-fluorothiadiazolyl)	-t-butyl
CGT (a and b)	-5-(4-fluorothiadiazolyl)	-iso-butyl
CGU (a and b)	-5-(4-fluorothiadiazolyl)	-sec-butyl
CGV (a and b)	-5-(4-fluorothiadiazolyl)	-cyclohexyl
CGW (a and b)	-5-(4-fluorothiadiazolyl)	-t-butoxy
CGX (a and b)	-5-(4-fluorothiadiazolyl)	-isopropoxy
CGY (a and b)	-5-(4-fluorothiadiazolyl)	$-CF_3$
CGZ (a and b)	-5-(4-fluorothiadiazolyl)	$-CH_2CF_3$
CHA (a and b)	-5-(4-fluorothiadiazolyl)	$-OCF_3$
CHB (a and b)	-5-(4-fluorothiadiazolyl)	-Cl
CHC (a and b)	-5-(4-fluorothiadiazolyl)	-Br
CHD (a and b)	-5-(4-fluorothiadiazolyl)	-I

CHE (a and b)	-5-(4-fluorothiadiazolyl)	-n-butyl
CHF (a and b)	-5-(4-fluorothiadiazolyl)	-n-propyl

wherein "a" means that the carbon atom of the piperazino group to which the methyl group is attached is in the R configuration and "b" means that the carbon of the piperazino group to which the methyl group is attached is in the S configuration

Table 6



XI

and pharmaceutically acceptable salts thereof, wherein:

Compound	Ar	R^9
CHG	-2-(3-chloropyridyl)	-t-butyl
CHH	-2-(3-chloropyridyl)	-iso-butyl
CHI	-2-(3-chloropyridyl)	-sec-butyl
CHJ	-2-(3-chloropyridyl)	-cyclohexyl
CHK	-2-(3-chloropyridyl)	-t-butoxy
CHL	-2-(3-chloropyridyl)	-isopropoxy
CHM	-2-(3-chloropyridyl)	$-CF_3$
CHN	-2-(3-chloropyridyl)	$-CH_2CF_3$
CHO	-2-(3-chloropyridyl)	$-OCF_3$
CHP	-2-(3-chloropyridyl)	-Cl
CHQ	-2-(3-chloropyridyl)	-Br
CHR	-2-(3-chloropyridyl)	-I
CHS	-2-(3-chloropyridyl)	-n-butyl
CHT	-2-(3-chloropyridyl)	-n-propyl
CHU	-2-(3-fluoropyridyl)	-t-butyl

CHV	-2-(3-fluoropyridyl)	-iso-butyl
CHW	-2-(3-fluoropyridyl)	-sec-butyl
CHX	-2-(3-fluoropyridyl)	-cyclohexyl
CHY	-2-(3-fluoropyridyl)	-t-butoxy
CHZ	-2-(3-fluoropyridyl)	-isopropoxy
CIA	-2-(3-fluoropyridyl)	$-CF_3$
CIB	-2-(3-fluoropyridyl)	$-CH_2CF_3$
CIC	-2-(3-fluoropyridyl)	$-OCF_3$
CID	-2-(3-fluoropyridyl)	-Cl
CIE	-2-(3-fluoropyridyl)	-Br
CIF	-2-(3-fluoropyridyl)	-I
CIG	-2-(3-fluoropyridyl)	-n-butyl
CIH	-2-(3-fluoropyridyl)	-n-propyl
CII	-2-(3-methylpyridyl)	-t-butyl
CIJ	-2-(3-methylpyridyl)	-iso-butyl
CIK	-2-(3-methylpyridyl)	-sec-butyl
CIL	-2-(3-methylpyridyl)	-cyclohexyl
CIM	-2-(3-methylpyridyl)	-t-butoxy
CIN	-2-(3-methylpyridyl)	-isopropoxy
CIO	-2-(3-methylpyridyl)	$-CF_3$
CIP	-2-(3-methylpyridyl)	$-CH_2CF_3$
CIQ	-2-(3-methylpyridyl)	$-OCF_3$
CIR	-2-(3-methylpyridyl)	-Cl
CIS	-2-(3-methylpyridyl)	-Br
CIT	-2-(3-methylpyridyl)	-I
CIU	-2-(3-methylpyridyl)	-n-butyl
CIV	-2-(3-methylpyridyl)	-n-propyl
CIW	-2-(3-CF_3-pyridyl)	-t-butyl
CIX	-2-(3-CF_3-pyridyl)	-iso-butyl

CIY	-2-(3-CF_3-pyridyl)	-sec-butyl
CIZ	-2-(3-CF_3-pyridyl)	-cyclohexyl
CJA	-2-(3-CF_3-pyridyl)	-t-butoxy
CJB	-2-(3-CF_3-pyridyl)	-isopropoxy
CJC	-2-(3-CF_3-pyridyl)	-CF_3
CJD	-2-(3-CF_3-pyridyl)	-CH_2CF_3
CJE	-2-(3-CF_3-pyridyl)	-OCF_3
CJF	-2-(3-CF_3-pyridyl)	-Cl
CJG	-2-(3-CF_3-pyridyl)	-Br
CJH	-2-(3-CF_3-pyridyl)	-I
CJI	-2-(3-CF_3-pyridyl)	-n-butyl
CJJ	-2-(3-CF_3-pyridyl)	-n-propyl
CJK	-2-(3-CHF_2-pyridyl)	-t-butyl
CJL	-2-(3-CHF_2-pyridyl)	-iso-butyl
CJM	-2-(3-CHF_2-pyridyl)	-sec-butyl
CJN	-2-(3-CHF_2-pyridyl)	-cyclohexyl
CJO	-2-(3-CHF_2-pyridyl)	-t-butoxy
CJP	-2-(3-CHF_2-pyridyl)	-isopropoxy
CJQ	-2-(3-CHF_2-pyridyl)	-CF_3
CJR	-2-(3-CHF_2-pyridyl)	-CH_2CF_3
CJS	-2-(3-CHF_2-pyridyl)	-OCF_3
CJT	-2-(3-CHF_2-pyridyl)	-Cl
CJU	-2-(3-CHF_2-pyridyl)	-Br
CJV	-2-(3-CHF_2-pyridyl)	-I
CJW	-2-(3-CHF_2-pyridyl)	-n-butyl
CJX	-2-(3-CHF_2-pyridyl)	-n-propyl
CJY	-2-(3-hydroxypyridyl)	-t-butyl
CJZ	-2-(3-hydroxypyridyl)	-iso-butyl
CKA	-2-(3-hydroxypyridyl)	-sec-butyl

CKB	-2-(3-hydroxypyridyl)	-cyclohexyl
CKC	-2-(3-hydroxypyridyl)	-t-butoxy
CKD	-2-(3-hydroxypyridyl)	-isopropoxy
CKE	-2-(3-hydroxypyridyl)	$-CF_3$
CKF	-2-(3-hydroxypyridyl)	$-CH_2CF_3$
CKG	-2-(3-hydroxypyridyl)	$-OCF_3$
CKH	-2-(3-hydroxypyridyl)	-Cl
CKI	-2-(3-hydroxypyridyl)	-Br
CKJ	-2-(3-hydroxypyridyl)	-I
CKK	-2-(3-hydroxypyridyl)	-n-butyl
CKL	-2-(3-hydroxypyridyl)	-n-propyl
CKM	-2-(3-nitropyridyl)	-t-butyl
CKN	-2-(3-nitropyridyl)	-iso-butyl
CKO	-2-(3-nitropyridyl)	-sec-butyl
CKP	-2-(3-nitropyridyl)	-cyclohexyl
CKQ	-2-(3-nitropyridyl)	-t-butoxy
CKR	-2-(3-nitropyridyl)	-isopropoxy
CKS	-2-(3-nitropyridyl)	$-CF_3$
CKT	-2-(3-nitropyridyl)	$-CH_2CF_3$
CKU	-2-(3-nitropyridyl)	$-OCF_3$
CKV	-2-(3-nitropyridyl)	-Cl
CKW	-2-(3-nitropyridyl)	-Br
CKX	-2-(3-nitropyridyl)	-I
CKY	-2-(3-nitropyridyl)	-n-butyl
CKZ	-2-(3-nitropyridyl)	-n-propyl
CLA	-2-(3-cyanopyridyl)	-t-butyl
CLB	-2-(3-cyanopyridyl)	-iso-butyl
CLC	-2-(3-cyanopyridyl)	-sec-butyl
CLD	-2-(3-cyanopyridyl)	-cyclohexyl

CLE	-2-(3-cyanopyridyl)	-t-butoxy
CLF	-2-(3-cyanopyridyl)	-isopropoxy
CLG	-2-(3-cyanopyridyl)	$-CF_3$
CLH	-2-(3-cyanopyridyl)	$-CH_2CF_3$
CLI	-2-(3-cyanopyridyl)	$-OCF_3$
CLJ	-2-(3-cyanopyridyl)	-Cl
CLK	-2-(3-cyanopyridyl)	-Br
CLL	-2-(3-cyanopyridyl)	-I
CLM	-2-(3-cyanopyridyl)	-n-butyl
CLN	-2-(3-cyanopyridyl)	-n-propyl
CLO	-2-(3-bromopyridyl)	-t-butyl
CLP	-2-(3-bromopyridyl)	-iso-butyl
CLQ	-2-(3-bromopyridyl)	-sec-butyl
CLR	-2-(3-bromopyridyl)	-cyclohexyl
CLS	-2-(3-bromopyridyl)	-t-butoxy
CLT	-2-(3-bromopyridyl)	-isopropoxy
CLU	-2-(3-bromopyridyl)	$-CF_3$
CLV	-2-(3-bromopyridyl)	$-CH_2CF_3$
CLW	-2-(3-bromopyridyl)	$-OCF_3$
CLX	-2-(3-bromopyridyl)	-Cl
CLY	-2-(3-bromopyridyl)	-Br
CLZ	-2-(3-bromopyridyl)	-I
CMA	-2-(3-bromopyridyl)	-n-butyl
CMB	-2-(3-bromopyridyl)	-n-propyl
CMC	-2-(3-iodopyridyl)	-t-butyl
CMD	-2-(3-iodopyridyl)	-iso-butyl
CME	-2-(3-iodopyridyl)	-sec-butyl
CMF	-2-(3-iodopyridyl)	-cyclohexyl
CMG	-2-(3-iodopyridyl)	-t-butoxy

CMH	-2-(3-iodopyridyl)	-isopropoxy
CMI	-2-(3-iodopyridyl)	$-CF_3$
CMJ	-2-(3-iodopyridyl)	$-CH_2CF_3$
CMK	-2-(3-iodopyridyl)	$-OCF_3$
CML	-2-(3-iodopyridyl)	-Cl
CMM	-2-(3-iodopyridyl)	-Br
CMN	-2-(3-iodopyridyl)	-I
CMO	-2-(3-iodopyridyl)	-n-butyl
CMP	-2-(3-iodopyridyl)	-n-propyl
CMQ	-4-(5-chloropyrimidinyl)	-t-butyl
CMR	-4-(5-chloropyrimidinyl)	-iso-butyl
CMS	-4-(5-chloropyrimidinyl)	-sec-butyl
CMT	-4-(5-chloropyrimidinyl)	-cyclohexyl
CMU	-4-(5-chloropyrimidinyl)	-t-butoxy
CMV	-4-(5-chloropyrimidinyl)	-isopropoxy
CMW	-4-(5-chloropyrimidinyl)	$-CF_3$
CMX	-4-(5-chloropyrimidinyl)	$-CH_2CF_3$
CMY	-4-(5-chloropyrimidinyl)	$-OCF_3$
CMZ	-4-(5-chloropyrimidinyl)	-Cl
CNA	-4-(5-chloropyrimidinyl)	-Br
CNB	-4-(5-chloropyrimidinyl)	-I
CNC	-4-(5-chloropyrimidinyl)	-n-butyl
CND	-4-(5-chloropyrimidinyl)	-n-propyl
CNE	-4-(5-methylpyrimidinyl)	-t-butyl
CNF	-4-(5-methylpyrimidinyl)	-iso-butyl
CNG	-4-(5-methylpyrimidinyl)	-sec-butyl
CNH	-4-(5-methylpyrimidinyl)	-cyclohexyl
CNI	-4-(5-methylpyrimidinyl)	-t-butoxy
CNJ	-4-(5-methylpyrimidinyl)	-isopropoxy

CNK	-4-(5-methylpyrimidinyl)	$-CF_3$
CNL	-4-(5-methylpyrimidinyl)	$-CH_2CF_3$
CNM	-4-(5-methylpyrimidinyl)	$-OCF_3$
CNN	-4-(5-methylpyrimidinyl)	-Cl
CNO	-4-(5-methylpyrimidinyl)	-Br
CNP	-4-(5-methylpyrimidinyl)	-I
CNQ	-4-(5-methylpyrimidinyl)	-n-butyl
CNR	-4-(5-methylpyrimidinyl)	-n-propyl
CNS	-4-(5-fluoropyrimidinyl)	-t-butyl
CNT	-4-(5-fluoropyrimidinyl)	-iso-butyl
CNU	-4-(5-fluoropyrimidinyl)	-sec-butyl
CNV	-4-(5-fluoropyrimidinyl)	-cyclohexyl
CNW	-4-(5-fluoropyrimidinyl)	-t-butoxy
CNX	-4-(5-fluoropyrimidinyl)	-isopropoxy
CNY	-4-(5-fluoropyrimidinyl)	$-CF_3$
CNZ	-4-(5-fluoropyrimidinyl)	$-CH_2CF_3$
COA	-4-(5-fluoropyrimidinyl)	$-OCF_3$
COB	-4-(5-fluoropyrimidinyl)	-Cl
COC	-4-(5-fluoropyrimidinyl)	-Br
COD	-4-(5-fluoropyrimidinyl)	-I
COE	-4-(5-fluoropyrimidinyl)	-n-butyl
COF	-4-(5-fluoropyrimidinyl)	-n-propyl
COG	-2-(3-chloropyrazinyl)	-t-butyl
COH	-2-(3-chloropyrazinyl)	-iso-butyl
COI	-2-(3-chloropyrazinyl)	-sec-butyl
COJ	-2-(3-chloropyrazinyl)	-cyclohexyl
COK	-2-(3-chloropyrazinyl)	-t-butoxy
COL	-2-(3-chloropyrazinyl)	-isopropoxy
COM	-2-(3-chloropyrazinyl)	$-CF_3$

CON	-2-(3-chloropyrazinyl)	$-CH_2CF_3$
COO	-2-(3-chloropyrazinyl)	$-OCF_3$
COP	-2-(3-chloropyrazinyl)	-Cl
COQ	-2-(3-chloropyrazinyl)	-Br
COR	-2-(3-chloropyrazinyl)	-I
COS	-2-(3-chloropyrazinyl)	-n-butyl
COT	-2-(3-chloropyrazinyl)	-n-propyl
COU	-2-(3-methylpyrazinyl)	-t-butyl
COV	-2-(3-methylpyrazinyl)	-iso-butyl
COW	-2-(3-methylpyrazinyl)	-sec-butyl
COX	-2-(3-methylpyrazinyl)	-cyclohexyl
COY	-2-(3-methylpyrazinyl)	-t-butoxy
COZ	-2-(3-methylpyrazinyl)	-isopropoxy
CPA	-2-(3-methylpyrazinyl)	$-CF_3$
CPB	-2-(3-methylpyrazinyl)	$-CH_2CF_3$
CPC	-2-(3-methylpyrazinyl)	$-OCF_3$
CPD	-2-(3-methylpyrazinyl)	-Cl
CPE	-2-(3-methylpyrazinyl)	-Br
CPF	-2-(3-methylpyrazinyl)	-I
CPG	-2-(3-methylpyrazinyl)	-n-butyl
CPH	-2-(3-methylpyrazinyl)	-n-propyl
CPI	-2-(3-fluoropyrazinyl)	-t-butyl
CPJ	-2-(3-fluoropyrazinyl)	-iso-butyl
CPK	-2-(3-fluoropyrazinyl)	-sec-butyl
CPL	-2-(3-fluoropyrazinyl)	-cyclohexyl
CPM	-2-(3-fluoropyrazinyl)	-t-butoxy
CPN	-2-(3-fluoropyrazinyl)	-isopropoxy
CPO	-2-(3-fluoropyrazinyl)	$-CF_3$
CPP	-2-(3-fluoropyrazinyl)	$-CH_2CF_3$

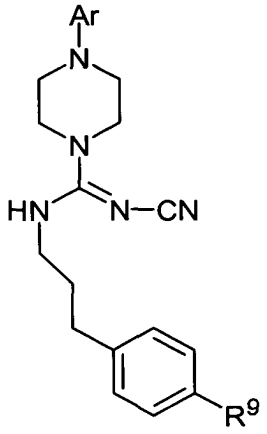
CPQ	-2-(3-fluoropyrazinyl)	$-OCF_3$
CPR	-2-(3-fluoropyrazinyl)	-Cl
CPS	-2-(3-fluoropyrazinyl)	-Br
CPT	-2-(3-fluoropyrazinyl)	-I
CPU	-2-(3-fluoropyrazinyl)	-n-butyl
CPV	-2-(3-fluoropyrazinyl)	-n-propyl
CPW	-3-(4-chloropyridazinyl)	-t-butyl
CPX	-3-(4-chloropyridazinyl)	-iso-butyl
CPY	-3-(4-chloropyridazinyl)	-sec-butyl
CPZ	-3-(4-chloropyridazinyl)	-cyclohexyl
CQA	-3-(4-chloropyridazinyl)	-t-butoxy
CQB	-3-(4-chloropyridazinyl)	-isopropoxy
CQC	-3-(4-chloropyridazinyl)	$-CF_3$
CQD	-3-(4-chloropyridazinyl)	$-CH_2CF_3$
CQE	-3-(4-chloropyridazinyl)	$-OCF_3$
CQF	-3-(4-chloropyridazinyl)	-Cl
CQG	-3-(4-chloropyridazinyl)	-Br
CQH	-3-(4-chloropyridazinyl)	-I
CQI	-3-(4-chloropyridazinyl)	-n-butyl
CQJ	-3-(4-chloropyridazinyl)	-n-propyl
CQK	-3-(4-methylpyridazinyl)	-t-butyl
CQL	-3-(4-methylpyridazinyl)	-iso-butyl
CQM	-3-(4-methylpyridazinyl)	-sec-butyl
CQN	-3-(4-methylpyridazinyl)	-cyclohexyl
CQO	-3-(4-methylpyridazinyl)	-t-butoxy
CQP	-3-(4-methylpyridazinyl)	-isopropoxy
CQQ	-3-(4-methylpyridazinyl)	$-CF_3$
CQR	-3-(4-methylpyridazinyl)	$-CH_2CF_3$
CQS	-3-(4-methylpyridazinyl)	$-OCF_3$

CQT	-3-(4-methylpyridazinyl)	-Cl
CQU	-3-(4-methylpyridazinyl)	-Br
CQV	-3-(4-methylpyridazinyl)	-I
CQW	-3-(4-methylpyridazinyl)	-n-butyl
CQX	-3-(4-methylpyridazinyl)	-n-propyl
CQY	-3-(4-fluoropyridazinyl)	-t-butyl
CQZ	-3-(4-fluoropyridazinyl)	-iso-butyl
CRA	-3-(4-fluoropyridazinyl)	-sec-butyl
CRB	-3-(4-fluoropyridazinyl)	-cyclohexyl
CRC	-3-(4-fluoropyridazinyl)	-t-butoxy
CRD	-3-(4-fluoropyridazinyl)	-isopropoxy
CRE	-3-(4-fluoropyridazinyl)	$-CF_3$
CRF	-3-(4-fluoropyridazinyl)	$-CH_2CF_3$
CRG	-3-(4-fluoropyridazinyl)	$-OCF_3$
CRH	-3-(4-fluoropyridazinyl)	-Cl
CRI	-3-(4-fluoropyridazinyl)	-Br
CRJ	-3-(4-fluoropyridazinyl)	-I
CRK	-3-(4-fluoropyridazinyl)	-n-butyl
CRL	-3-(4-fluoropyridazinyl)	-n-propyl
CRM	-5-(4-chlorothiadiazolyl)	-t-butyl
CRN	-5-(4-chlorothiadiazolyl)	-iso-butyl
CRO	-5-(4-chlorothiadiazolyl)	-sec-butyl
CRP	-5-(4-chlorothiadiazolyl)	-cyclohexyl
CRQ	-5-(4-chlorothiadiazolyl)	-t-butoxy
CRR	-5-(4-chlorothiadiazolyl)	-isopropoxy
CRS	-5-(4-chlorothiadiazolyl)	$-CF_3$
CRT	-5-(4-chlorothiadiazolyl)	$-CH_2CF_3$
CRU	-5-(4-chlorothiadiazolyl)	$-OCF_3$
CRV	-5-(4-chlorothiadiazolyl)	-Cl

CRW	-5-(4-chlorothiadiazolyl)	-Br
CRX	-5-(4-chlorothiadiazolyl)	-I
CRY	-5-(4-chlorothiadiazolyl)	-n-butyl
CRZ	-5-(4-chlorothiadiazolyl)	-n-propyl
CSA	-5-(4-methylthiadiazolyl)	-t-butyl
CSB	-5-(4-methylthiadiazolyl)	-iso-butyl
CSC	-5-(4-methylthiadiazolyl)	-sec-butyl
CSD	-5-(4-methylthiadiazolyl)	-cyclohexyl
CSE	-5-(4-methylthiadiazolyl)	-t-butoxy
CSF	-5-(4-methylthiadiazolyl)	-isopropoxy
CSG	-5-(4-methylthiadiazolyl)	$-CF_3$
CSH	-5-(4-methylthiadiazolyl)	$-CH_2CF_3$
CSI	-5-(4-methylthiadiazolyl)	$-OCF_3$
CSJ	-5-(4-methylthiadiazolyl)	-Cl
CSK	-5-(4-methylthiadiazolyl)	-Br
CSL	-5-(4-methylthiadiazolyl)	-I
CSM	-5-(4-methylthiadiazolyl)	-n-butyl
CSN	-5-(4-methylthiadiazolyl)	-n-propyl
CSO	-5-(4-fluorothiadiazolyl)	-t-butyl
CSP	-5-(4-fluorothiadiazolyl)	-iso-butyl
CSQ	-5-(4-fluorothiadiazolyl)	-sec-butyl
CSR	-5-(4-fluorothiadiazolyl)	-cyclohexyl
CSS	-5-(4-fluorothiadiazolyl)	-t-butoxy
CST	-5-(4-fluorothiadiazolyl)	-isopropoxy
CSU	-5-(4-fluorothiadiazolyl)	$-CF_3$
CSV	-5-(4-fluorothiadiazolyl)	$-CH_2CF_3$
CSW	-5-(4-fluorothiadiazolyl)	$-OCF_3$
CSX	-5-(4-fluorothiadiazolyl)	-Cl
CSY	-5-(4-fluorothiadiazolyl)	-Br

CSZ	-5-(4-fluorothiadiazolyl)	-I
CTA	-5-(4-fluorothiadiazolyl)	-n-butyl
CTB	-5-(4-fluorothiadiazolyl)	-n-propyl

Table 7



and pharmaceutically acceptable salts thereof, wherein:

Compound	Ar	R^9
CTC	-2-(3-chloropyridyl)	-t-butyl
CTD	-2-(3-chloropyridyl)	-iso-butyl
CTE	-2-(3-chloropyridyl)	-sec-butyl
CTF	-2-(3-chloropyridyl)	-cyclohexyl
CTG	-2-(3-chloropyridyl)	-t-butoxy
CTH	-2-(3-chloropyridyl)	-isopropoxy
CTI	-2-(3-chloropyridyl)	$-CF_3$
CTJ	-2-(3-chloropyridyl)	$-CH_2CF_3$
CTK	-2-(3-chloropyridyl)	$-OCF_3$
CTL	-2-(3-chloropyridyl)	-Cl
CTM	-2-(3-chloropyridyl)	-Br
CTN	-2-(3-chloropyridyl)	-I
CTO	-2-(3-chloropyridyl)	-n-butyl
CTP	-2-(3-chloropyridyl)	-n-propyl
CTQ	-2-(3-fluoropyridyl)	-t-butyl
CTR	-2-(3-fluoropyridyl)	-iso-butyl
CTS	-2-(3-fluoropyridyl)	-sec-butyl
CTT	-2-(3-fluoropyridyl)	-cyclohexyl

CTU	-2-(3-fluoropyridyl)	-t-butoxy
CTV	-2-(3-fluoropyridyl)	-isopropoxy
CTW	-2-(3-fluoropyridyl)	$-CF_3$
CTX	-2-(3-fluoropyridyl)	$-CH_2CF_3$
CTY	-2-(3-fluoropyridyl)	$-OCF_3$
CTZ	-2-(3-fluoropyridyl)	-Cl
CUA	-2-(3-fluoropyridyl)	-Br
CUB	-2-(3-fluoropyridyl)	-I
CUC	-2-(3-fluoropyridyl)	-n-butyl
CUD	-2-(3-fluoropyridyl)	-n-propyl
CUE	-2-(3-methylpyridyl)	-t-butyl
CUF	-2-(3-methylpyridyl)	-iso-butyl
CUG	-2-(3-methylpyridyl)	-sec-butyl
CUH	-2-(3-methylpyridyl)	-cyclohexyl
CUI	-2-(3-methylpyridyl)	-t-butoxy
CUJ	-2-(3-methylpyridyl)	-isopropoxy
CUK	-2-(3-methylpyridyl)	$-CF_3$
CUL	-2-(3-methylpyridyl)	$-CH_2CF_3$
CUM	-2-(3-methylpyridyl)	$-OCF_3$
CUN	-2-(3-methylpyridyl)	-Cl
CUO	-2-(3-methylpyridyl)	-Br
CUP	-2-(3-methylpyridyl)	-I
CUQ	-2-(3-methylpyridyl)	-n-butyl
CUR	-2-(3-methylpyridyl)	-n-propyl
CUS	-2-(3-CF_3-pyridyl)	-t-butyl
CUT	-2-(3-CF_3-pyridyl)	-iso-butyl
CUU	-2-(3-CF_3-pyridyl)	-sec-butyl
CUV	-2-(3-CF_3-pyridyl)	-cyclohexyl
CUW	-2-(3-CF_3-pyridyl)	-t-butoxy

CUX	-2-(3-CF_3-pyridyl)	-isopropoxy
CUY	-2-(3-CF_3-pyridyl)	-CF_3
CUZ	-2-(3-CF_3-pyridyl)	-CH_2CF_3
CVA	-2-(3-CF_3-pyridyl)	-OCF_3
CVB	-2-(3-CF_3-pyridyl)	-Cl
CVC	-2-(3-CF_3-pyridyl)	-Br
CVD	-2-(3-CF_3-pyridyl)	-I
CVE	-2-(3-CF_3-pyridyl)	-n-butyl
CVF	-2-(3-CF_3-pyridyl)	-n-propyl
CVG	-2-(3-CHF_2-pyridyl)	-t-butyl
CVH	-2-(3-CHF_2-pyridyl)	-iso-butyl
CVI	-2-(3-CHF_2-pyridyl)	-sec-butyl
CVJ	-2-(3-CHF_2-pyridyl)	-cyclohexyl
CVK	-2-(3-CHF_2-pyridyl)	-t-butoxy
CVL	-2-(3-CHF_2-pyridyl)	-isopropoxy
CVM	-2-(3-CHF_2-pyridyl)	-CF_3
CVN	-2-(3-CHF_2-pyridyl)	-CH_2CF_3
CVO	-2-(3-CHF_2-pyridyl)	-OCF_3
CVP	-2-(3-CHF_2-pyridyl)	-Cl
CVQ	-2-(3-CHF_2-pyridyl)	-Br
CVR	-2-(3-CHF_2-pyridyl)	-I
CVS	-2-(3-CHF_2-pyridyl)	-n-butyl
CVT	-2-(3-CHF_2-pyridyl)	-n-propyl
CVU	-2-(3-hydroxypyridyl)	-t-butyl
CVV	-2-(3-hydroxypyridyl)	-iso-butyl
CVW	-2-(3-hydroxypyridyl)	-sec-butyl
CVX	-2-(3-hydroxypyridyl)	-cyclohexyl
CVY	-2-(3-hydroxypyridyl)	-t-butoxy
CVZ	-2-(3-hydroxypyridyl)	-isopropoxy

CWA	-2-(3-hydroxypyridyl)	$-CF_3$
CWB	-2-(3-hydroxypyridyl)	$-CH_2CF_3$
CWC	-2-(3-hydroxypyridyl)	$-OCF_3$
CWD	-2-(3-hydroxypyridyl)	-Cl
CWE	-2-(3-hydroxypyridyl)	-Br
CWF	-2-(3-hydroxypyridyl)	-I
CWG	-2-(3-hydroxypyridyl)	-n-butyl
CWH	-2-(3-hydroxypyridyl)	-n-propyl
CWI	-2-(3-nitropyridyl)	-t-butyl
CWJ	-2-(3-nitropyridyl)	-iso-butyl
CWK	-2-(3-nitropyridyl)	-sec-butyl
CWL	-2-(3-nitropyridyl)	-cyclohexyl
CWM	-2-(3-nitropyridyl)	-t-butoxy
CWN	-2-(3-nitropyridyl)	-isopropoxy
CWO	-2-(3-nitropyridyl)	$-CF_3$
CWP	-2-(3-nitropyridyl)	$-CH_2CF_3$
CWQ	-2-(3-nitropyridyl)	$-OCF_3$
CWR	-2-(3-nitropyridyl)	-Cl
CWS	-2-(3-nitropyridyl)	-Br
CWT	-2-(3-nitropyridyl)	-I
CWU	-2-(3-nitropyridyl)	-n-butyl
CWV	-2-(3-nitropyridyl)	-n-propyl
CWW	-2-(3-cyanopyridyl)	-t-butyl
CWX	-2-(3-cyanopyridyl)	-iso-butyl
CWY	-2-(3-cyanopyridyl)	-sec-butyl
CWZ	-2-(3-cyanopyridyl)	-cyclohexyl
CXA	-2-(3-cyanopyridyl)	-t-butoxy
CXB	-2-(3-cyanopyridyl)	-isopropoxy
CXC	-2-(3-cyanopyridyl)	$-CF_3$

CXD	-2-(3-cyanopyridyl)	$-CH_2CF_3$
CXE	-2-(3-cyanopyridyl)	$-OCF_3$
CXF	-2-(3-cyanopyridyl)	-Cl
CXG	-2-(3-cyanopyridyl)	-Br
CXH	-2-(3-cyanopyridyl)	-I
CXI	-2-(3-cyanopyridyl)	-n-butyl
CXJ	-2-(3-cyanopyridyl)	-n-propyl
CXK	-2-(3-bromopyridyl)	-t-butyl
CXL	-2-(3-bromopyridyl)	-iso-butyl
CXM	-2-(3-bromopyridyl)	-sec-butyl
CXN	-2-(3-bromopyridyl)	-cyclohexyl
CXO	-2-(3-bromopyridyl)	-t-butoxy
CXP	-2-(3-bromopyridyl)	-isopropoxy
CXQ	-2-(3-bromopyridyl)	$-CF_3$
CXR	-2-(3-bromopyridyl)	$-CH_2CF_3$
CXS	-2-(3-bromopyridyl)	$-OCF_3$
CXT	-2-(3-bromopyridyl)	-Cl
CXU	-2-(3-bromopyridyl)	-Br
CXV	-2-(3-bromopyridyl)	-I
CXW	-2-(3-bromopyridyl)	-n-butyl
CXX	-2-(3-bromopyridyl)	-n-propyl
CXY	-2-(3-iodopyridyl)	-t-butyl
CXZ	-2-(3-iodopyridyl)	-iso-butyl
CYA	-2-(3-iodopyridyl)	-sec-butyl
CYB	-2-(3-iodopyridyl)	-cyclohexyl
CYC	-2-(3-iodopyridyl)	-t-butoxy
CYD	-2-(3-iodopyridyl)	-isopropoxy
CYE	-2-(3-iodopyridyl)	$-CF_3$
CYF	-2-(3-iodopyridyl)	$-CH_2CF_3$

CYG	-2-(3-iodopyridyl)	$-OCF_3$
CYH	-2-(3-iodopyridyl)	-Cl
CYI	-2-(3-iodopyridyl)	-Br
CYJ	-2-(3-iodopyridyl)	-I
CYK	-2-(3-iodopyridyl)	-n-butyl
CYL	-2-(3-iodopyridyl)	-n-propyl
CYM	-4-(5-chloropyrimidinyl)	-t-butyl
CYN	-4-(5-chloropyrimidinyl)	-iso-butyl
CYO	-4-(5-chloropyrimidinyl)	-sec-butyl
CYP	-4-(5-chloropyrimidinyl)	-cyclohexyl
CYQ	-4-(5-chloropyrimidinyl)	-t-butoxy
CYR	-4-(5-chloropyrimidinyl)	-isopropoxy
CYS	-4-(5-chloropyrimidinyl)	$-CF_3$
CYT	-4-(5-chloropyrimidinyl)	$-CH_2CF_3$
CYU	-4-(5-chloropyrimidinyl)	$-OCF_3$
CYV	-4-(5-chloropyrimidinyl)	-Cl
CYW	-4-(5-chloropyrimidinyl)	-Br
CYX	-4-(5-chloropyrimidinyl)	-I
CYY	-4-(5-chloropyrimidinyl)	-n-butyl
CYZ	-4-(5-chloropyrimidinyl)	-n-propyl
CZA	-4-(5-methylpyrimidinyl)	-t-butyl
CZB	-4-(5-methylpyrimidinyl)	-iso-butyl
CZC	-4-(5-methylpyrimidinyl)	-sec-butyl
CZD	-4-(5-methylpyrimidinyl)	-cyclohexyl
CZE	-4-(5-methylpyrimidinyl)	-t-butoxy
CZF	-4-(5-methylpyrimidinyl)	-isopropoxy
CZG	-4-(5-methylpyrimidinyl)	$-CF_3$
CZH	-4-(5-methylpyrimidinyl)	$-CH_2CF_3$
CZI	-4-(5-methylpyrimidinyl)	$-OCF_3$

CZJ	-4-(5-methylpyrimidinyl)	-Cl
CZK	-4-(5-methylpyrimidinyl)	-Br
CZL	-4-(5-methylpyrimidinyl)	-I
CZM	-4-(5-methylpyrimidinyl)	-n-butyl
CZN	-4-(5-methylpyrimidinyl)	-n-propyl
CZO	-4-(5-fluoropyrimidinyl)	-t-butyl
CZP	-4-(5-fluoropyrimidinyl)	-iso-butyl
CZQ	-4-(5-fluoropyrimidinyl)	-sec-butyl
CZR	-4-(5-fluoropyrimidinyl)	-cyclohexyl
CZS	-4-(5-fluoropyrimidinyl)	-t-butoxy
CZT	-4-(5-fluoropyrimidinyl)	-isopropoxy
CZU	-4-(5-fluoropyrimidinyl)	$-CF_3$
CZV	-4-(5-fluoropyrimidinyl)	$-CH_2CF_3$
CZW	-4-(5-fluoropyrimidinyl)	$-OCF_3$
CZX	-4-(5-fluoropyrimidinyl)	-Cl
CZY	-4-(5-fluoropyrimidinyl)	-Br
CZZ	-4-(5-fluoropyrimidinyl)	-I
DAA	-4-(5-fluoropyrimidinyl)	-n-butyl
DAB	-4-(5-fluoropyrimidinyl)	-n-propyl
DAC	-2-(3-chloropyrazinyl)	-t-butyl
DAD	-2-(3-chloropyrazinyl)	-iso-butyl
DAE	-2-(3-chloropyrazinyl)	-sec-butyl
DAF	-2-(3-chloropyrazinyl)	-cyclohexyl
DAG	-2-(3-chloropyrazinyl)	-t-butoxy
DAH	-2-(3-chloropyrazinyl)	-isopropoxy
DAI	-2-(3-chloropyrazinyl)	$-CF_3$
DAJ	-2-(3-chloropyrazinyl)	$-CH_2CF_3$
DAK	-2-(3-chloropyrazinyl)	$-OCF_3$
DAL	-2-(3-chloropyrazinyl)	-Cl

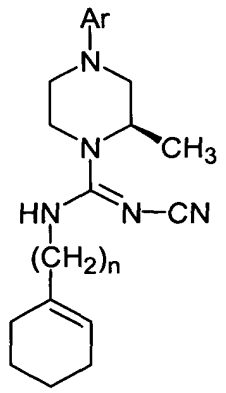
DAM	-2-(3-chloropyrazinyl)	-Br
DAN	-2-(3-chloropyrazinyl)	-I
DAO	-2-(3-chloropyrazinyl)	-n-butyl
DAP	-2-(3-chloropyrazinyl)	-n-propyl
DAQ	-2-(3-methylpyrazinyl)	-t-butyl
DAR	-2-(3-methylpyrazinyl)	-iso-butyl
DAS	-2-(3-methylpyrazinyl)	-sec-butyl
DAT	-2-(3-methylpyrazinyl)	-cyclohexyl
DAU	-2-(3-methylpyrazinyl)	-t-butoxy
DAV	-2-(3-methylpyrazinyl)	-isopropoxy
DAW	-2-(3-methylpyrazinyl)	$-CF_3$
DAX	-2-(3-methylpyrazinyl)	$-CH_2CF_3$
DAY	-2-(3-methylpyrazinyl)	$-OCF_3$
DAZ	-2-(3-methylpyrazinyl)	-Cl
DBA	-2-(3-methylpyrazinyl)	-Br
DBB	-2-(3-methylpyrazinyl)	-I
DBC	-2-(3-methylpyrazinyl)	-n-butyl
DBD	-2-(3-methylpyrazinyl)	-n-propyl
DBE	-2-(3-fluoropyrazinyl)	-t-butyl
DBF	-2-(3-fluoropyrazinyl)	-iso-butyl
DBG	-2-(3-fluoropyrazinyl)	-sec-butyl
DBH	-2-(3-fluoropyrazinyl)	-cyclohexyl
DBI	-2-(3-fluoropyrazinyl)	-t-butoxy
DBJ	-2-(3-fluoropyrazinyl)	-isopropoxy
DBK	-2-(3-fluoropyrazinyl)	$-CF_3$
DBL	-2-(3-fluoropyrazinyl)	$-CH_2CF_3$
DBM	-2-(3-fluoropyrazinyl)	$-OCF_3$
DBN	-2-(3-fluoropyrazinyl)	-Cl
DBO	-2-(3-fluoropyrazinyl)	-Br

DBP	-2-(3-fluoropyrazinyl)	-I
DBQ	-2-(3-fluoropyrazinyl)	-n-butyl
DBR	-2-(3-fluoropyrazinyl)	-n-propyl
DBS	-3-(4-chloropyridazinyl)	-t-butyl
DBT	-3-(4-chloropyridazinyl)	-iso-butyl
DBU	-3-(4-chloropyridazinyl)	-sec-butyl
DBV	-3-(4-chloropyridazinyl)	-cyclohexyl
DBW	-3-(4-chloropyridazinyl)	-t-butoxy
DBX	-3-(4-chloropyridazinyl)	-isopropoxy
DBY	-3-(4-chloropyridazinyl)	$-CF_3$
DBZ	-3-(4-chloropyridazinyl)	$-CH_2CF_3$
DCA	-3-(4-chloropyridazinyl)	$-OCF_3$
DCB	-3-(4-chloropyridazinyl)	-Cl
DCC	-3-(4-chloropyridazinyl)	-Br
DCD	-3-(4-chloropyridazinyl)	-I
DCE	-3-(4-chloropyridazinyl)	-n-butyl
DCF	-3-(4-chloropyridazinyl)	-n-propyl
DCG	-3-(4-methylpyridazinyl)	-t-butyl
DCH	-3-(4-methylpyridazinyl)	-iso-butyl
DCI	-3-(4-methylpyridazinyl)	-sec-butyl
DCJ	-3-(4-methylpyridazinyl)	-cyclohexyl
DCK	-3-(4-methylpyridazinyl)	-t-butoxy
DCL	-3-(4-methylpyridazinyl)	-isopropoxy
DCM	-3-(4-methylpyridazinyl)	$-CF_3$
DCN	-3-(4-methylpyridazinyl)	$-CH_2CF_3$
DCO	-3-(4-methylpyridazinyl)	$-OCF_3$
DCP	-3-(4-methylpyridazinyl)	-Cl
DCQ	-3-(4-methylpyridazinyl)	-Br
DCR	-3-(4-methylpyridazinyl)	-I

DCS	-3-(4-methylpyridazinyl)	-n-butyl
DCT	-3-(4-methylpyridazinyl)	-n-propyl
DCU	-3-(4-fluoropyridazinyl)	-t-butyl
DCV	-3-(4-fluoropyridazinyl)	-iso-butyl
DCW	-3-(4-fluoropyridazinyl)	-sec-butyl
DCX	-3-(4-fluoropyridazinyl)	-cyclohexyl
DCY	-3-(4-fluoropyridazinyl)	-t-butoxy
DCZ	-3-(4-fluoropyridazinyl)	-isopropoxy
DDA	-3-(4-fluoropyridazinyl)	$-CF_3$
DDB	-3-(4-fluoropyridazinyl)	$-CH_2CF_3$
DDC	-3-(4-fluoropyridazinyl)	$-OCF_3$
DDD	-3-(4-fluoropyridazinyl)	-Cl
DDE	-3-(4-fluoropyridazinyl)	-Br
DDF	-3-(4-fluoropyridazinyl)	-I
DDG	-3-(4-fluoropyridazinyl)	-n-butyl
DDH	-3-(4-fluoropyridazinyl)	-n-propyl
DDI	-5-(4-chlorothiadiazolyl)	-t-butyl
DDJ	-5-(4-chlorothiadiazolyl)	-iso-butyl
DDK	-5-(4-chlorothiadiazolyl)	-sec-butyl
DDL	-5-(4-chlorothiadiazolyl)	-cyclohexyl
DDM	-5-(4-chlorothiadiazolyl)	-t-butoxy
DDN	-5-(4-chlorothiadiazolyl)	-isopropoxy
DDO	-5-(4-chlorothiadiazolyl)	$-CF_3$
DDP	-5-(4-chlorothiadiazolyl)	$-CH_2CF_3$
DDQ	-5-(4-chlorothiadiazolyl)	$-OCF_3$
DDR	-5-(4-chlorothiadiazolyl)	-Cl
DDS	-5-(4-chlorothiadiazolyl)	-Br
DDT	-5-(4-chlorothiadiazolyl)	-I
DDU	-5-(4-chlorothiadiazolyl)	-n-butyl

DDV	-5-(4-chlorothiadiazolyl)	-n-propyl
DDW	-5-(4-methylthiadiazolyl)	-t-butyl
DDX	-5-(4-methylthiadiazolyl)	-iso-butyl
DDY	-5-(4-methylthiadiazolyl)	-sec-butyl
DDZ	-5-(4-methylthiadiazolyl)	-cyclohexyl
DEA	-5-(4-methylthiadiazolyl)	-t-butoxy
DEB	-5-(4-methylthiadiazolyl)	-isopropoxy
DEC	-5-(4-methylthiadiazolyl)	$-CF_3$
DED	-5-(4-methylthiadiazolyl)	$-CH_2CF_3$
DEE	-5-(4-methylthiadiazolyl)	$-OCF_3$
DEF	-5-(4-methylthiadiazolyl)	-Cl
DEG	-5-(4-methylthiadiazolyl)	-Br
DEH	-5-(4-methylthiadiazolyl)	-I
DEI	-5-(4-methylthiadiazolyl)	-n-butyl
DEJ	-5-(4-methylthiadiazolyl)	-n-propyl
DEK	-5-(4-fluorothiadiazolyl)	-t-butyl
DEL	-5-(4-fluorothiadiazolyl)	-iso-butyl
DEM	-5-(4-fluorothiadiazolyl)	-sec-butyl
DEN	-5-(4-fluorothiadiazolyl)	-cyclohexyl
DEO	-5-(4-fluorothiadiazolyl)	-t-butoxy
DEP	-5-(4-fluorothiadiazolyl)	-isopropoxy
DEQ	-5-(4-fluorothiadiazolyl)	$-CF_3$
DER	-5-(4-fluorothiadiazolyl)	$-CH_2CF_3$
DES	-5-(4-fluorothiadiazolyl)	$-OCF_3$
DET	-5-(4-fluorothiadiazolyl)	-Cl
DEU	-5-(4-fluorothiadiazolyl)	-Br
DEV	-5-(4-fluorothiadiazolyl)	-I
DEW	-5-(4-fluorothiadiazolyl)	-n-butyl
DEX	-5-(4-fluorothiadiazolyl)	-n-propyl

Table 8



and pharmaceutically acceptable salts thereof, wherein:

Compound	Ar	n
DEY	-2-(3-chloropyridyl)	2
DEZ	-2-(3-fluoropyridyl)	2
DFA	-2-(3-methylpyridyl)	2
DFB	-2-(3-CF_3-pyridyl)	2
DFC	-2-(3-CHF_2-pyridyl)	2
DFD	-2-(3-hydroxypyridyl)	2
DFE	-2-(3-nitropyridyl)	2
DFF	-2-(3-cyanopyridyl)	2
DFG	-2-(3-bromopyridyl)	2
DFH	-2-(3-iodopyridyl)	2
DFI	-4-(5-chloropyrimidinyl)	2
DFJ	-4-(5-methylpyrimidinyl)	2
DFK	-4-(5-fluoropyrimidinyl)	2
DFL	-2-(3-chloropyrazinyl)	2
DFM	-2-(3-methylpyrazinyl)	2
DFN	-2-(3-fluoropyrazinyl)	2
DFO	-3-(4-chloropyridazinyl)	2
DFP	-3-(4-methylpyridazinyl)	2

DFQ	-3-(4-fluoropyridazinyl)	2
DFR	-5-(4-chlorothiadiazolyl)	2
DFS	-5-(4-methylthiadiazolyl)	2
DFT	-5-(4-fluorothiadiazolyl)	2
DFU	-2-(3-chloropyridyl)	3
DFV	-2-(3-fluoropyridyl)	3
DFW	-2-(3-methylpyridyl)	3
DFX	-2-(3-CF_3-pyridyl)	3
DFY	-2-(3-CHF_2-pyridyl)	3
DFZ	-2-(3-hydroxypyridyl)	3
DGA	-2-(3-nitropyridyl)	3
DGB	-2-(3-cyanopyridyl)	3
DGC	-2-(3-bromopyridyl)	3
DGD	-2-(3-iodopyridyl)	3
DGE	-4-(5-chloropyrimidinyl)	3
DGF	-4-(5-methylpyrimidinyl)	3
DGG	-4-(5-fluoropyrimidinyl)	3
DGH	-2-(3-chloropyrazinyl)	3
DGI	-2-(3-methylpyrazinyl)	3
DGJ	-2-(3-fluoropyrazinyl)	3
DGK	-3-(4-chloropyridazinyl)	3
DGL	-3-(4-methylpyridazinyl)	3
DGM	-3-(4-fluoropyridazinyl)	3
DGN	-5-(4-chlorothiadiazolyl)	3
DGO	-5-(4-methylthiadiazolyl)	3
DGP	-5-(4-fluorothiadiazolyl)	3

4.17 DEFINITIONS

As used herein, the terms used above having following meaning:

"-(C_1-C_{10})alkyl" means a straight chain or branched non-cyclic hydrocarbon having from 1 to 10 carbon atoms. Representative straight chain -(C_1-C_{10})alkyls include -methyl, -ethyl, -n-propyl, -n-butyl, -n-pentyl, -n-hexyl, -n-heptyl, -n-octyl, -n-nonly and -n-decyl. Representative branched -(C_1-C_{10})alkyls include -isopropyl, -sec-butyl, -isobutyl, -tert-butyl, -isopentyl, -neopentyl, 1-methylbutyl, 2-methylbutyl, 3-methylbutyl, 1,1-dimethylpropyl, 1,2-dimethylpropyl, 1-methylpentyl, 2-methylpentyl, 3-methylpentyl, 4-methylpentyl, 1-ethylbutyl, 2-ethylbutyl, 3-ethylbutyl, 1,1-dimethtylbutyl, 1,2-dimethylbutyl, 1,3-dimethylbutyl, 2,2-dimethylbutyl, 2,3-dimethylbutyl and 3,3-dimethylbutyl. -isopropyl, -*sec*-butyl, -isobutyl, 1-methylhexyl, 2-methylhexyl, 3-methylhexyl, 4-methylhexyl, 5-methylhexyl, 1,2-dimethylpentyl, 1,3-dimethylpentyl, 1,2-dimethylhexyl, 1,3-dimethylhexyl, 3,3-dimethylhexyl, 1,2-dimethylheptyl, 1,3-dimethylheptyl, and 3,3-dimethylheptyl.

"-(C_1-C_6)alkyl" means a straight chain or branched non-cyclic hydrocarbon having from 1 to 6 carbon atoms. Representative straight chain -(C_1-C_6)alkyls include -methyl, -ethyl, -n-propyl, -n-butyl, -n-pentyl and -n-hexyl. Representative branched -(C_1-C_6)alkyls include -isopropyl, -sec-butyl, -isobutyl, -tert-butyl, -isopentyl, -neopentyl, 1-methylbutyl, 2-methylbutyl, 3-methylbutyl, 1,1-dimethylpropyl, 1,2-dimethylpropyl, 1-methylpentyl, 2-methylpentyl, 3-methylpentyl, 4-methylpentyl, 1-ethylbutyl, 2-ethylbutyl, 3-ethylbutyl, 1,1-dimethtylbutyl, 1,2-dimethylbutyl, 1,3-dimethylbutyl, 2,2-dimethylbutyl, 2,3-dimethylbutyl and 3,3-dimethylbutyl.

"-(C_2-C_{10})alkenyl" means a straight chain or branched non-cyclic hydrocarbon having from 2 to 10 carbon atoms and including at least one carbon-carbon double bond. Representative straight chain and branched (C_2-C_{10})alkenyls include -vinyl, -allyl, -1-butenyl, -2-butenyl, -isobutylenyl, -1-pentenyl, -2-pentenyl, -3-methyl-1-butenyl, -2-methyl-2-butenyl, -2,3-dimethyl-2-butenyl, -1-hexenyl, -2-hexenyl, -3-hexenyl, -1-heptenyl, -2-heptenyl, -3-heptenyl, -1-octenyl, -2-octenyl, -3-octenyl, -1-nonenyl, -2-nonenyl, -3-nonenyl, -1-decenyl, -2-decenyl, -3-decenyl and the like.

"-(C_2-C_6)alkenyl" means a straight chain or branched non-cyclic hydrocarbon having from 2 to 6 carbon atoms and including at least one carbon-carbon double bond. Representative straight chain and branched (C_2-C_6)alkenyls include -vinyl, -allyl, -1-butenyl, -2-butenyl, -isobutylenyl, -1-pentenyl, -2-pentenyl, -3-methyl-1-butenyl, -2-methyl-2-butenyl, -2,3-dimethyl-2-butenyl, -1-hexenyl, 2-hexenyl, 3-hexenyl and the like.

"-(C_2-C_{10})alkynyl" means a straight chain or branched non-cyclic hydrocarbon having from 2 to 10 carbon atoms and including at lease one carbon-carbon triple bond. Representative straight chain and branched -(C_2-C_{10})alkynyls include -acetylenyl, -propynyl, -1-butynyl, -2-butynyl, -1-pentynyl, -2-pentynyl, -3-methyl-1-butynyl, -4-pentynyl, -1-hexynyl, -2-hexynyl, -5-hexynyl, -1-heptynyl, -2-heptynyl, -6-heptynyl, -1-octynyl, -2-octynyl, -7-octynyl, -1-nonynyl, -2-nonynyl, -8-nonynyl, -1-decynyl, -2-decynyl, -9-decynyl and the like.

"-(C_2-C_6)alkynyl" means a straight chain or branched non-cyclic hydrocarbon having from 2 to 6 carbon atoms and including at lease one carbon-carbon triple bond. Representative straight chain and branched (C_2-C_6)alkynyls include -acetylenyl, -propynyl, -1-butynyl, -2-butynyl, -1-pentynyl, -2-pentynyl, -3-methyl-1-butynyl, -4-pentynyl, -1-hexynyl, -2-hexynyl, -5-hexynyl and the like.

"-(C_3-C_{10})cycloalkyl" means a saturated cyclic hydrocarbon having from 3 to 10 carbon atoms. Representative (C_3-C_{10})cycloalkyls are -cyclopropyl, -cyclobutyl, -cyclopentyl, -cyclohexyl, -cycloheptyl, -cyclooctyl, -cyclononyl and -cyclodecyl.

"-(C_3-C_8)cycloalkyl" means a saturated cyclic hydrocarbon having from 3 to 8 carbon atoms. Representative (C_3-C_8)cycloalkyls include -cyclopropyl, -cyclobutyl, -cyclopentyl, -cyclohexyl, -cycloheptyl and -cyclooctyl.

"-(C_8-C_{14})bicycloalkyl" means a bi-cyclic hydrocarbon ring system having from 8 to 14 carbon atoms and at least one saturated cyclic alkyl ring. Representative -(C_8-C_{14})bicycloalkyls include -indanyl, -1,2,3,4-tetrahydronaphthyl, -5,6,7,8-tetrahydronaphthyl, -perhydronaphthyl and the like.

"-(C_8-C_{14})tricycloalkyl" means a tri-cyclic hydrocarbon ring system having from 8 to 14 carbon atoms and at least one saturated ring. Representative -(C_8-C_{14})tricycloalkyls include -pyrenyl, -1,2,3,4-tetrahydroanthracenyl, -perhydroanthracenyl -aceanthreneyl, -1,2,3,4-tetrahydropenanthrenyl, -5,6,7,8-tetrahydrophenanthrenyl,

-perhydrophenanthrenyl and the like.

"-(C_5-C_{10})cycloalkenyl" means a cyclic non-aromatic hydrocarbon having at least one carbon-carbon double bond in the cyclic system and from 5 to 10 carbon atoms. Representative (C_5-C_{10})cycloalkenyls include -cyclopentenyl, -cyclopentadienyl, -cyclohexenyl, -cyclohexadienyl,-cycloheptenyl, -cycloheptadienyl, -cycloheptatrienyl, -cyclooctenyl, -cyclooctadienyl, -cyclooctatrienyl, -cyclooctatetraenyl, -cyclononenyl -cyclononadienyl, -cyclodecenyl, -cyclodecadienyl and the like.

"-(C_5-C_8)cycloalkenyl" means a cyclic non-aromatic hydrocarbon having at least one carbon-carbon double bond in the cyclic system and from 5 to 8 carbon atoms. Representative (C_5-C_8)cycloalkenyls include -cyclopentenyl, -cyclopentadienyl, -cyclohexenyl, -cyclohexadienyl, -cycloheptenyl, -cycloheptadienyl, -cycloheptatrienyl, -cyclooctenyl, -cyclooctadienyl, -cyclooctatrienyl, -cyclooctatetraenyl and the like.

"-(C_8-C_{14})bicycloalkenyl" means a bi-cyclic hydrocarbon ring system having at least one carbon-carbon double bond in each ring and from 8 to 14 carbon atoms. Representative -(C_8-C_{14})bicycloalkenyls include -indenyl, -pentalenyl, -naphthalenyl, -azulenyl, -heptalenyl, -1,2,7,8-tetrahydronaphthalenyl and the like.

"-(C_8-C_{14})tricycloalkenyl" means a tri-cyclic hydrocarbon ring system having at least one carbon-carbon double bond in each ring and from 8 to 14 carbon atoms. Representative -(C_8-C_{14})tricycloalkenyls include -anthracenyl, -phenanthrenyl, -phenalenyl, -acenaphthalenyl, *as*-indacenyl, *s*-indacenyl and the like.

"-(C_3-C_7)heterocycle" or "-(C_3-C_7)heterocyclo" means a 3- to 7-membered monocyclic heterocyclic ring which is either saturated, unsaturated non-aromatic, or aromatic. A 3-membered -(C_3-C_7)heterocycle can contain up to 3 heteroatoms, and a 4- to 7-membered -(C_3-C_7)heterocycle can contain up to 4 heteroatoms. Each heteroatom is independently selected from nitrogen, which can be quaternized; oxygen; and sulfur, including sulfoxide and sulfone. The -(C_3-C_7)heterocycle can be attached via a nitrogen, sulfur, or carbon atom. Representative -(C_3-C_7)heterocycles include pyridyl, furyl, thiophenyl, pyrrolyl, oxazolyl, imidazolyl, thiazolyl, thiadiazolyl, isoxazolyl, pyrazolyl, isothiazolyl, pyridazinyl, pyrimidinyl, pyrazinyl, triazinyl, morpholinyl, pyrrolidinonyl, pyrrolidinyl, piperidinyl, piperazinyl, hydantoinyl, valerolactamyl, oxiranyl, oxetanyl, tetrahydrofuranyl,

tetrahydropyranyl, tetrahydropyrindinyl, tetrahydropyrimidinyl, tetrahydrothiophenyl, tetrahydrothiopyranyl and the like.

"-(C_3-C_5)heterocycle" or "-(C_3-C_5)heterocyclo" means a 3- to 5-membered monocyclic heterocyclic ring which is either saturated, unsaturated non-aromatic, or aromatic. A 3-membered -(C_3-C_7)heterocycle can contain up to 3 heteroatoms, and a 4- to 5-membered -(C_3-C_5)heterocycle can contain up to 4 heteroatoms. Each heteroatom is independently selected from nitrogen, which can be quaternized; oxygen; and sulfur, including sulfoxide and sulfone. The -(C_3-C_5)heterocycle can be attached via a nitrogen, sulfur, or carbon atom. Representative -(C_3-C_5)heterocycles include furyl, thiophenyl, pyrrolyl, oxazolyl, imidazolyl, thiazolyl, isoxazolyl, pyrazolyl, isothiazolyl, triazinyl, pyrrolidinonyl, pyrrolidinyl, hydantoinyl, oxiranyl, oxetanyl, tetrahydrofuranyl, tetrahydrothiophenyl and the like.

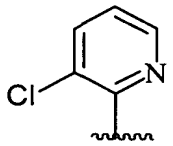
"-(C_7-C_{10})bicycloheterocycle" or "-(C_7-C_{10})bicycloheterocyclo" means a 7- to 10-membered bicyclic, heterocyclic ring which is either saturated, unsaturated non-aromatic, or aromatic. A -(C_7-C_{10})bicycloheterocycle contains from 1 to 4 heteroatoms independently selected from nitrogen, which can be quaternized; oxygen; and sulfur, including sulfoxide and sulfone. The (C_7-C_{10})bicycloheterocycle can be attached via a nitrogen, sulfur, or carbon atom. Representative -(C_7-C_{10})bicycloheterocycles include -quinolinyl, -isoquinolinyl, -chromonyl, -coumarinyl, -indolyl, -indolizinyl, -benzo[b]furanyl, -benzo[b]thiophenyl, -indazolyl, -purinyl, -4H-quinolizinyl, -isoquinolyl, -quinolyl, -phthalazinyl, -naphthyridinyl, -carbazolyl, -β-carbolinyl and the like.

"-(C_{14})aryl" means a 14-membered aromatic carbocyclic moiety such as -anthryl or -phenanthryl.

"-(C_5-C_{10})heteroaryl" means an aromatic heterocycle ring of 5 to 10 members, including both mono- and bicyclic ring systems, wherein at least one carbon atom of one or both of the rings is replaced with a heteroatom independently selected from nitrogen, oxygen and sulfur. One or both of the -(C_5-C_{10})heteroaryl's rings contain at least one carbon atom. Representative (C_5-C_{10})heteroaryls include pyridyl, furyl, benzofuranyl, thiophenyl, benzothiophenyl, quinolinyl, pyrrolyl, indolyl, oxazolyl, benzoxazolyl, imidazolyl, benzimidazolyl, thiazolyl, benzothiazolyl, isoxazolyl, pyrazolyl, isothiazolyl, pyridazinyl, pyrimidinyl, pyrazinyl, thiadiazolyl, triazinyl, cinnolinyl, phthalazinyl, and quinazolinyl.

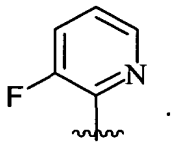
"-Halogen" or "-Halo" means -F, -Cl, -Br or -I.

The phrase "2-(3-chloropyridyl)" means



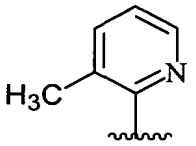
.

The phrase "2-(3-fluoropyridyl)" means



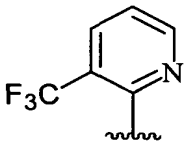
.

The phrase "2-(3-methylpyridyl)" means



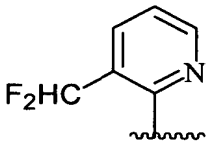
.

The phrase "2-(3-CF_3-methylpyridyl)" means



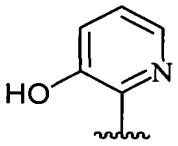
.

The phrase "2-(3-CHF_2-methylpyridyl)" means



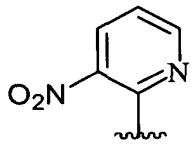
.

The phrase "2-(3-hydroxypyridyl)" means



.

The phrase "2-(3-nitropyridyl)" means



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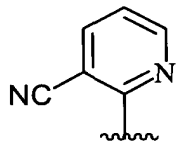
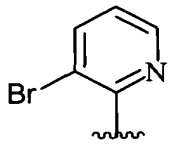
The phrase "2-(3-cyanopyridyl)" means



.

The phrase "2-(3-bromopyridyl)" means



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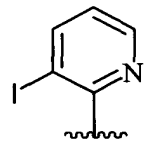
The phrase "2-(3-iodopyridyl)" means



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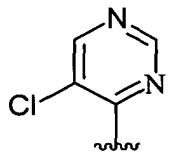
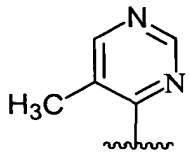
The phrase "4-(5-chloropyrimidinyl)" means



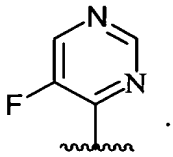
.

The phrase "4-(5-methylpyrimidinyl)" means

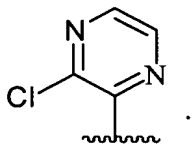


.

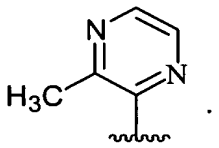
The phrase "4-(5-fluoropyrimidinyl)" means



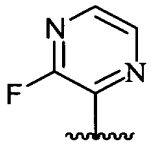
The phrase "2-(3-chloropyrazinyl)" means



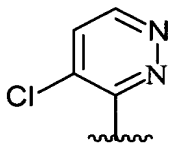
The phrase "2-(3-methylpyrazinyl)" means



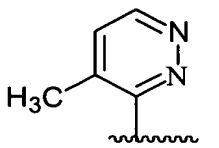
The phrase "2-(3-fluoropyrazinyl)" means



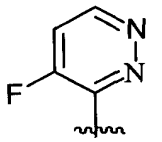
The phrase "3-(4-chloropyridazinyl)" means



The phrase "3-(4-methylpyridazinyl)" means



The phrase "3-(4-fluoropyridazinyl)" means



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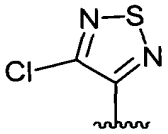
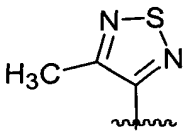
The phrase "5-(4-chlorothiadiazolyl)" means



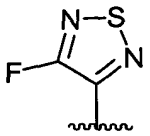
.

The phrase "5-(4-methylthiadiazolyl)" means



.

The phrase "5-(4-fluorothiadiazolyl)" means



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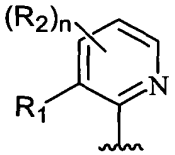
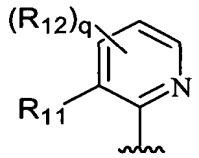
The phrase "pyridyl group" in connection with the Cyanoiminopiperazine Compounds of formula (I), (Ia), and (Ib) means



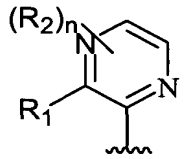
wherein R_1, R_2, and n are defined above for the Cyanoiminopiperazine Compounds of formula (I), (Ia), and (Ib).

The phrase "pyridyl group" in connection with the Cyanoiminopiperazine Compounds of formula (Ic) means



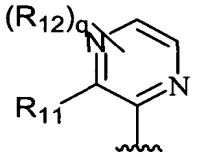
wherein R_{11}, R_{12}, and q are defined above for the Cyanoiminopiperazine Compounds of formula (Ic).

The phrase "pyrazinyl group" in connection with the Cyanoiminopiperazine Compounds of formula (II) means



wherein R_1, R_2, and n are defined above for the Cyanoiminopiperazine Compounds of formula (II).

The phrase "pyrazinyl group" in connection with the Cyanoiminopiperazine Compounds of formula (IIa) means

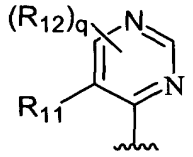


wherein R_1, R_2, and q are defined above for the Cyanoiminopiperazine Compounds of formula (IIa).

The phrase "pyrimidinyl group" in connection with the Cyanoiminopiperazine Compounds of formula (III), (IIIa), and (IIIb) means

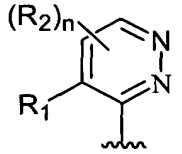
wherein R_1, R_2, and n are defined above for the Cyanoiminopiperazine Compounds of formula (III), (IIIa), and (IIIb).

The phrase "pyrimidinyl group" in connection with the Cyanoiminopiperazine Compounds of formula (IIIc) means



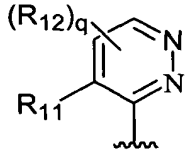
wherein R_{11}, R_{12}, and q are defined above for the Cyanoiminopiperazine Compounds of formula (IIIc).

The phrase "pyridizanyl group" in connection with the Cyanoiminopiperazine Compounds of formula (IV) means



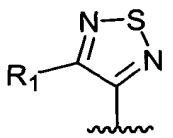
wherein R_1, R_2, and n are defined above for the Cyanoiminopiperazine Compounds of formula (IV).

The phrase "pyridizanyl group" in connection with the Cyanoiminopiperazine Compounds of formula (IVa) means



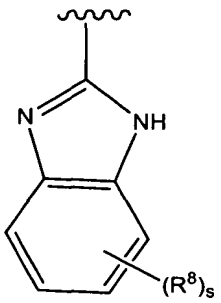
wherein R_{11}, R_{12}, and q are defined above for the Cyanoiminopiperazine Compounds of formula (IVa).

The phrase "thiadiazolyl group" means



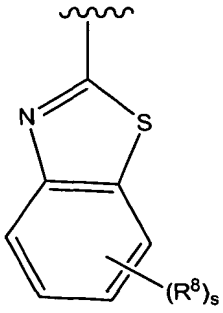
wherein R_1 is defined above for the Cyanoiminopiperazine Compounds of formula (V).

The phrase "benzothiazolyl group" means



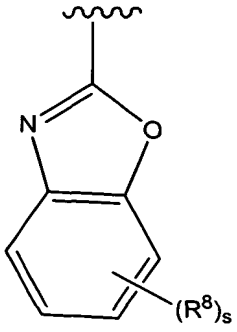
wherein R^8 and s are defined above for the Cyanoiminopiperazine Compounds of formulas (VI) and (VII).

The phrase "benzoimidazolyl group" means



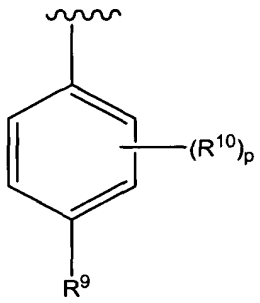
wherein R^8 and s are defined above for the Cyanoiminopiperazine Compounds of formulas (VI) and (VII).

The phrase "benzooxazolyl group" means

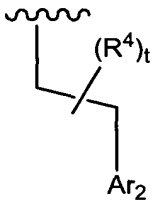


wherein R^8 and s are defined above for the Cyanoiminopiperazine Compounds of formulas (VI) and (VII).

The phrase "(R^9)-phenyl group" means

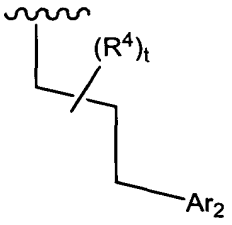


The phrase "phenethyl group" means an ethylene group attached to a terminal Ar_2 group, wherein one or each of two hydrogens of the ethylene group can optionally be substituted with an R^4 group. A phenethyl group is depicted below



wherein R^4, Ar_2, and t are defined above for the Cyanoiminopiperazine Compounds of formula (VI).

The phrase "phenpropyl group" an n-propylene group attached to a terminal Ar_2 group, wherein one or each of two hydrogens of the n-propylene group can optionally be substituted with an R^4 group. A phenpropyl group is depicted below



wherein R^4, Ar_2, and t are defined above for the Cyanoiminopiperazine Compounds of formula (VII).

The term "animal," includes, but is not limited to, a cow, monkey, horse, sheep, pig, chicken, turkey, quail, cat, dog, mouse, rat, rabbit, guinea pig and human.

The phrase "pharmaceutically acceptable salt," as used herein, is a salt formed from an acid and a basic nitrogen group of one of the Cyanoiminopiperazine Compounds. Illustrative salts include, but are not limited, to sulfate, citrate, acetate, oxalate, chloride, bromide, iodide, nitrate, bisulfate, phosphate, acid phosphate, isonicotinate, lactate, salicylate, acid citrate, tartrate, oleate, tannate, pantothenate, bitartrate, ascorbate, succinate, maleate, gentisinate, fumarate, gluconate, glucaronate, saccharate, formate, benzoate, glutamate, methanesulfonate, ethanesulfonate, benzenesulfonate, *p*-toluenesulfonate, and pamoate (*i.e.*, 1,1'-methylene-bis-(2-hydroxy-3-naphthoate)) salts. The term "pharmaceutically acceptable salt" also refers to a salt prepared from a Cyanoiminopiperazine Compound having an acidic functional group, such as a carboxylic acid functional group, and a pharmaceutically acceptable inorganic or organic base. Suitable bases include, but are not limited to, hydroxides of alkali metals such as sodium, potassium, and lithium; hydroxides of alkaline earth metal such as calcium and magnesium; hydroxides of other metals, such as aluminum and zinc; ammonia, and organic amines, such as unsubstituted or hydroxy-substituted mono-, di-, or trialkylamines; dicyclohexylamine; tributyl amine; pyridine; N-methyl,N-ethylamine; diethylamine; triethylamine; mono-, bis-, or tris-(2-hydroxy-lower alkyl amines), such as mono-, bis-, or tris-(2-hydroxyethyl)amine, 2-hydroxy-tert-butylamine, or tris-(hydroxymethyl)methylamine, N, N,-di-lower alkyl-N-(hydroxy lower alkyl)-amines, such as N,N,-dimethyl-N-(2-hydroxyethyl)amine, or tri-(2-hydroxyethyl)amine; N-methyl-D-glucamine; and amino acids such as arginine, lysine, and the like.

When a first group is "substituted with one or more" second groups, each of one or more of the first group's hydrogen atoms is replaced with a second group. In one embodiment, each carbon atom of a first group is independently substituted with one or two second groups. In another embodiment, each carbon atom of a first group is independently substituted with only one second group.

The term "UI" means urinary incontinence.

The term "IBD" means inflammatory-bowel disease.

The term "IBS" means irritable-bowel syndrome.

The term "DIEA" means diisopropylethylamine.

The term "DMSO" means dimethyl sulfoxide.

The term "DMF" means dimethyl formamide.

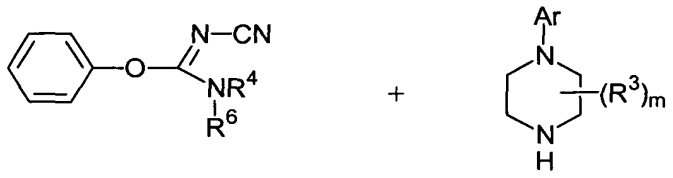
The term "DCM" means dichloromethane.

The phrase "treatment of" and "treating" includes the amelioration or cessation of a Condition or a symptom thereof.

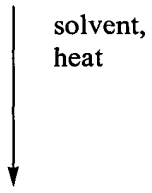
The phrase "prevention of" and "preventing" includes the avoidance of the onset of a Condition or a symptom thereof.

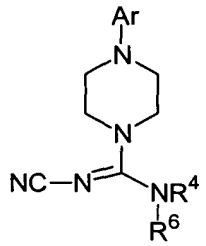
4.18 METHODS FOR MAKING THE CYANOIMINOPIPERAZINE COMPOUNDS

The Cyanoiminopiperazine Compounds can be made using conventional organic synthesis or by the following illustrative methods shown in the schemes below. The Cyanoiminopiperazine Compounds wherein A is NR^4 can be obtained by the following illustrative methods shown below in Scheme A:



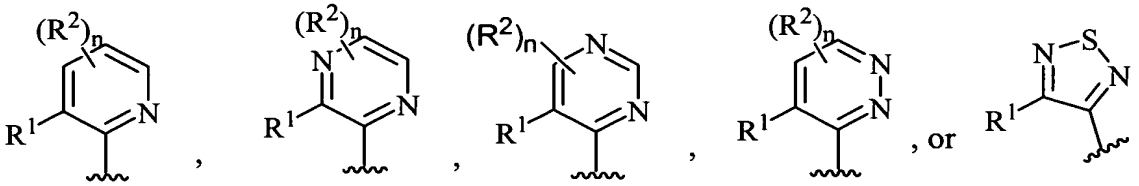
A **B**





Scheme A

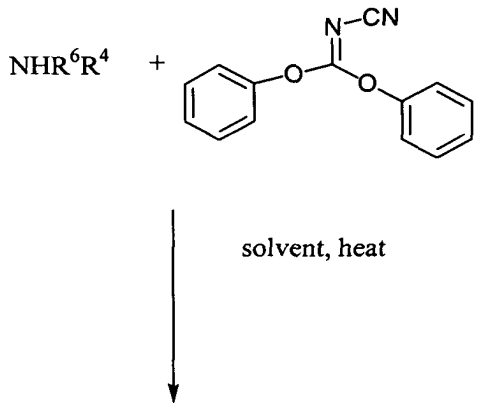
wherein R^3, R^4, R^6, and m are defined above for the Cyanoiminopiperazine Compounds and Ar is:



wherein R^1, R^2 and n are defined above.

A compound of formula **A** is reacted with a compound of formula **B** in an aprotic organic solvent such as diethyl ether, di-n-propyl ether, tetrahydrofuran, methylene chloride, or toluene at a temperature ranging from about room temperature to about the reflux temperature of the solvent for a period of about 0.5 h to about 24 h to provide a Cyanoiminopiperazine Compound wherein A is NR^4. In one embodiment, the aprotic organic solvent is di-n-propyl ether. In another embodiment, a reaction mixture of di-n-propyl ether, a compound of formula **A** and a compound of formula **B** is heated at a temperature of about 70° to about 80° C. In another embodiment, the reaction mixture of di-n-propyl ether, a compound of formula **A** and a compound of formula **B** is heated at a temperature of about at 75°C for about 12 h.

Compounds of formula **A** can be obtained as shown below in Scheme B:

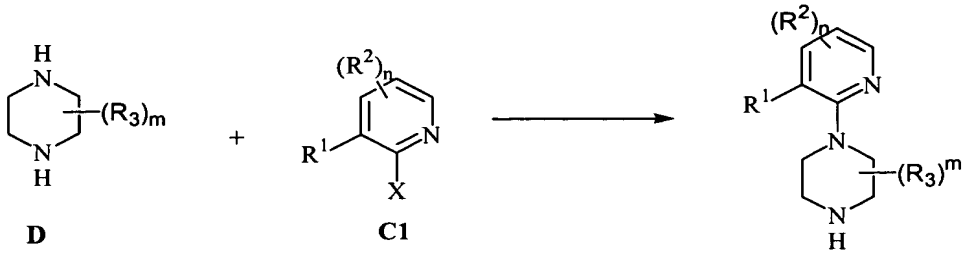


A

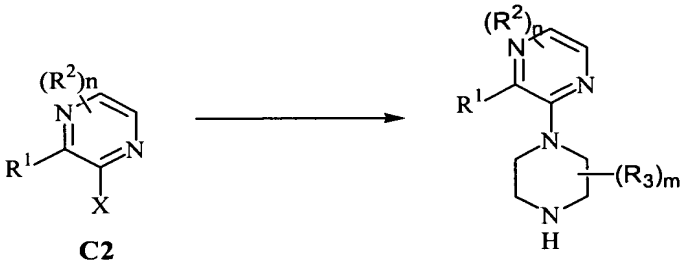
Scheme B

An amine of formula NHR^6R^4, wherein R^4 and R^6 are defined above, is reacted with diphenylcyanocabonimidate (commercially available from Sigma-Aldrich, St. Louis, MO (www.sigma-aldrich.com)) in an aprotic solvent such as diethyl ether, di-n-propyl ether, tetrahydrofuran, methylene chloride, or toluene to provide the compound of formula **A**. In one embodiment, the aprotic solvent is DCM and the reaction mixture of NHR^6R^4 and diphenylcyanocabonimidate is allowed to react at about room temperature. In another embodiment, the aprotic solvent is toluene and the reaction mixture of NHR^6R^4 and diphenylcyanocabonimidate is allowed to react at about 110°C. The NHR^6R^4 and diphenylcyanocabonimidate is typically allowed to react for a period of about 0.5 h to about 24 h. Typically the compound of formula **A** is used without further purification.

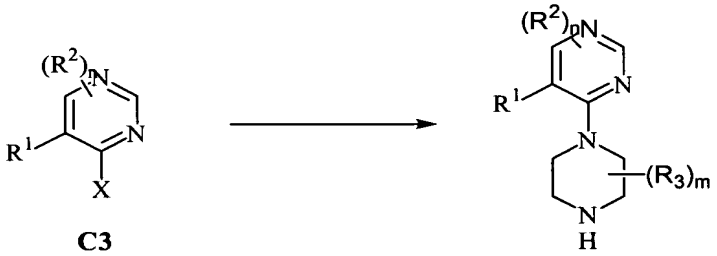
Compounds of formula **B** can be obtained as shown below in Scheme C:



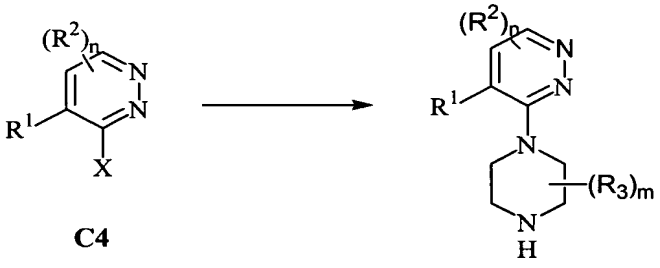
D **C1** **B1**



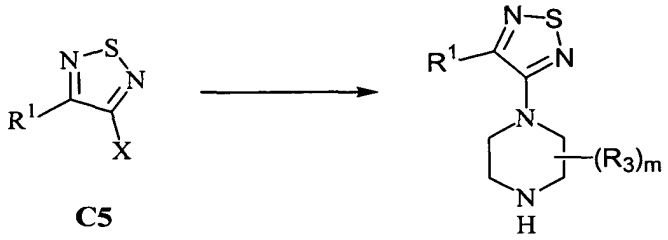
C2 **B2**



C3 **B3**



C4 **B4**



C5 B5

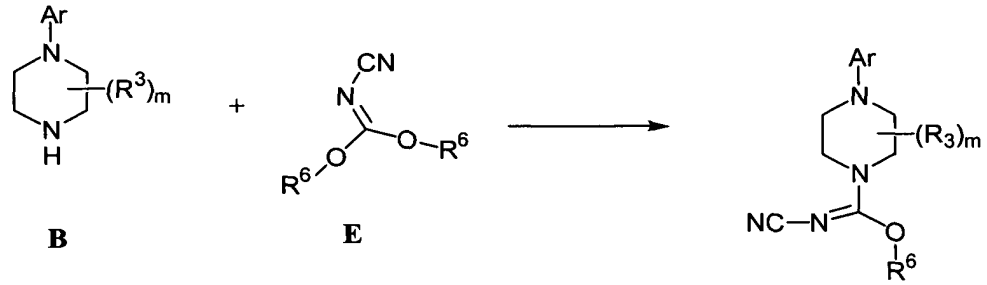
Scheme C

wherein R^1, R^2, R^3, m, and n are defined above and X is a halogen. In one embodiment, X is bromide, chloride or iodide.

A compound of formula **C1-C5** is reacted with a compound of formula **D** in an aprotic solvent in the presence of DIEA or triethylamine, optionally with heating, to provide compound **B**. Compound **B** is isolated from the reaction mixture and purified. In one embodiment, the reaction is purified using column chromatography or recrystallization.

Compounds of formula **C1-C5** and **D** are commercially available or can be prepared by methods well known to those skilled in the art. The compound of formula **D** wherein m is 0 is commercially available from Sigma-Aldrich, St. Louis, MO (www.sigma-aldrich.com).

The Cyanoiminopiperazine Compounds wherein A is -O- can be obtained as shown below in Scheme **D**.



B E

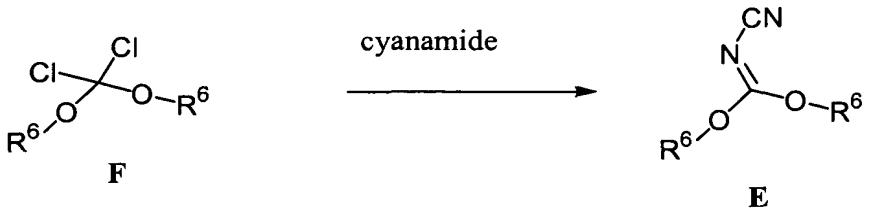
Scheme D

wherein R^3, R^6, m, and Ar are defined above for the Cyanoiminopiperazine Compounds.

A compound of formula **B** is reacted with a compound of formula **E** to provide the Cyanoiminopiperazine Compounds wherein A is -O-. Representative procedures for

reacting a compound of formula **B** with a compound of formula **E** are provided in T.D. Aicher et al., *J. Med. Chem.* 43(2):236-49 (2000) and German Patent No. 3336409.

The compound of formula **E** can be obtained as shown below in Scheme E.

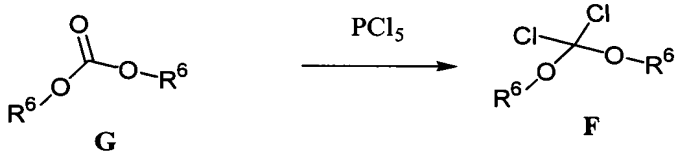


Scheme E

wherein R^6 is defined above.

The compound of formula **E** can be obtained by reacting a compound of formula **F** with cyanamide. Representative procedures for obtaining a compound of formula **E** from a compound of formula **F** are provided in R.L. Webb et al., *J. Heterocycl. Chem.* 19(5):1205-1206 (1982) and U.S. Patent No. 4,285,878 to Labaw et al.

The compound of formula **F** can be obtained as shown below in Scheme F.



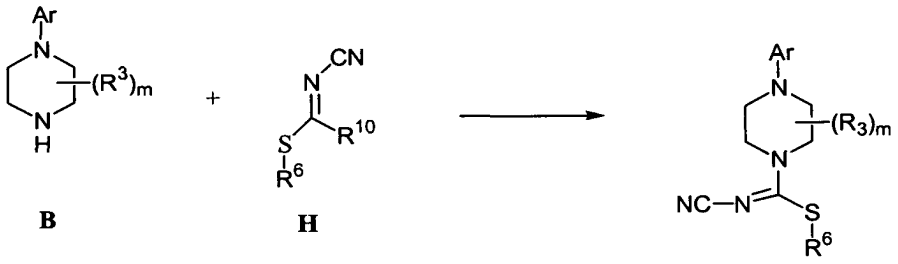
Scheme F

wherein R^6 is defined above.

The compound of formula **F** can be obtained by reacting a compound of formula **G** with PCl_5. A representative procedure for obtaining a compound of formula **F** from a compound of formula **G** is provided in R.L. Webb et al., *J. Heterocycl. Chem.* 19(5):1205-1206 (1982).

The compound of formula **G** can be obtained by reacting a compound of formula R^6-OH with $COCl_2$, triphosgene, or CO and a Pd catalyst as described in U.S. Patent No. 6,175,017 to H. Buyschi et al.; A. Gode et al., *Chemistry-A European Journal* 6(19):3522-30 (2000); or H. Yasuda et al., *Organometallics*, 21(6):1216-20 (2002), respectively. Compounds of formula R^6-OH are commercially available or can be prepared by methods well known to those skilled in the art.

The Cyanoiminopiperazine Compounds wherein A is -S- can be obtained as shown below in Scheme G.



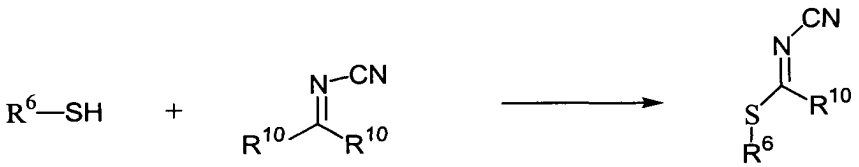
B **H**

Scheme G

wherein R^6, R^3, m, and Ar are defined above and R^{10} is $-SCH_3$ or $-O-C_6H_5$.

A compound of formula **B** is reacted with a compound of formula **H** to provide the Cyanoiminopiperazine Compounds wherein A is -S-. Representative procedures for reacting a compound of formula **B** with a compound of formula **H** are provided in T.D. Aicher et al., *J. Med. Chem.* 43(2):236-49 (2000) and Ger. Patent No. 3336409.

The compound of formula **H** can be obtained as shown below in Scheme H.



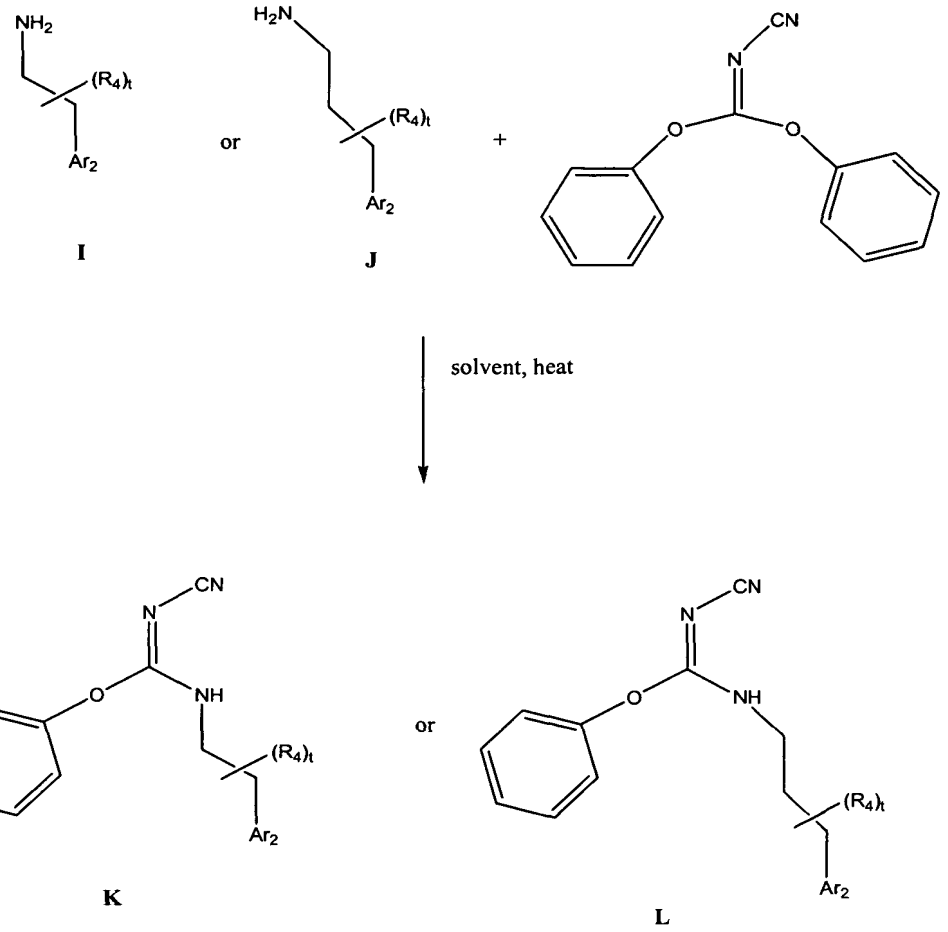
J **H**

Scheme H

wherein R^6 and R^{10} are defined above.

A thiol of formula R^6SH is reacted with a compound of formula **J** to provide the compound of formula **H**. Representative procedures for obtaining compounds of formula **J** and for obtaining the compound of formula **H** by reacting a thiol with a compound of formula **J** are provided in R.L. Webb et al., *J. Heterocycl. Chem.*, 24(1):275-78 (1987); I. Reid et al., *Liebigs Ann. Chem.* 6:599-601 (1988); and L.S. Wittenbrook et al., *J. Heterocycl. Chem.* 12(1):37-42 (1975). Compounds of formula R^6-SH are commercially available or can be prepared by methods well known to those skilled in the art.

The Cyanoiminopiperazine Compounds of formula VI and VII can be obtained as described below in Scheme **I**.



wherein Ar_2, R_4, and t are defined above.

Scheme I

An amine of formula **I** or an amine of formula **J** is reacted with diphenylcyanocabonimidate (commercially available from Sigma-Aldrich, St. Louis, MO (www.sigma-aldrich.com)) in an aprotic solvent such as diethyl ether, di-n-propyl ether, tetrahydrofuran, methylene chloride, or toluene to provide the compound of formula **K** or a compound of formula **L**, respectively. In one embodiment, the aprotic solvent is DCM and the reaction mixture of the amine of formula **I** or the amine of formula **J** and diphenylcyanocabonimidate is allowed to react at about room temperature. In another embodiment, the aprotic solvent is toluene and the reaction mixture of the amine of formula **I** or the amine of formula **J** and diphenylcyanocabonimidate is allowed to react at about 110°C. The amine of formula **I** or the amine of formula **J** and diphenylcyanocabonimidate is

typically allowed to react for a period of about 0.5 h to about 24 h. Typically the compound of formula **K** or the compound of formula **L** is used without further purification.

The compound of formula **K** or the compound of formula **L** is then reacted with a compound of formula **B,** obtained as described above in Scheme **B,** according to the procedure described above in Scheme **A** to provide the Cyanoiminopiperazine Compound of formula (VI) or (VII) , respectively.

4.19 THERAPEUTIC USES OF THE CYANOIMINOPIPERAZINE COMPOUNDS

In accordance with the invention, the Cyanoiminopiperazine Compounds are administered to an animal in need of treatment or prevention of pain, UI, an ulcer, IBD, IBS, an addictive disorder, Parkinson's disease, parkinsonism, anxiety, epilepsy, stroke, a seizure, a pruritic condition, psychosis, a cognitive disorder, a memory deficit, restricted brain function, Huntington's chorea, ALS, dementia, retinopathy, a muscle spasm, a migraine, vomiting, dyskinesia, or depression.

In one embodiment, an effective amount of a Cyanoiminopiperazine Compound can be used to treat or prevent any condition treatable or preventable by inhibiting VR1. Examples of conditions that are treatable or preventable by inhibiting VR1 include, but are not limited to, pain, UI, an ulcer, IBD, and IBS.

In another embodiment, an effective amount of a Cyanoiminopiperazine Compound can be used to treat or prevent any condition treatable or preventable by inhibiting mGluR5. Examples of conditions that are treatable or preventable by inhibiting mGluR5 include, but are not limited to, pain, an addictive disorder, Parkinson's disease, parkinsonism, anxiety, a pruritic condition, and psychosis.

In another embodiment, an effective amount of a Cyanoiminopiperazine Compound can be used to treat or prevent any condition treatable or preventable by inhibiting mGluR1. Examples of conditions that are treatable or preventable by inhibiting mGluR1 include, but are not limited to, pain, UI, an addictive disorder, Parkinson's disease, parkinsonism, anxiety, epilepsy, stroke, a seizure, a pruritic condition, psychosis, a cognitive disorder, a memory deficit, restricted brain function, Huntington's chorea, ALS, dementia, retinopathy, a muscle spasm, a migraine, vomiting, dyskinesia, and depression.

The Cyanoiminopiperazine Compounds can be used to treat or prevent acute or chronic pain. Examples of pain treatable or preventable using the Cyanoiminopiperazine Compounds include, but are not limited to, cancer pain, central pain, labor pain, myocardial infarction pain, pancreatic pain, colic pain, post-operative pain, headache pain, muscle pain, pain associated with intensive care, arthritic pain, neuropathic pain, and pain associated with a periodontal disease, including gingivitis and periodontitis.

The Cyanoiminopiperazine Compounds can also be used for inhibiting, preventing, or treating pain associated with inflammation or with an inflammatory disease in an animal. The pain to be inhibited, treated or prevented may be associated with inflammation associated with an inflammatory disease, which can arise where there is an inflammation of the body tissue, and which can be a local inflammatory response and/or a systemic inflammation. For example, the Cyanoiminopiperazine Compounds can be used to inhibit, treat, or prevent pain associated with inflammatory diseases including, but not limited to: organ transplant rejection; reoxygenation injury resulting from organ transplantation (see Grupp *et al.*, *J. Mol. Cell Cardiol.* 31:297-303 (1999)) including, but not limited to, transplantation of the heart, lung, liver, or kidney; chronic inflammatory diseases of the joints, including arthritis, rheumatoid arthritis, osteoarthritis and bone diseases associated with increased bone resorption; inflammatory lung diseases, such as asthma, adult respiratory distress syndrome, and chronic obstructive airway disease; inflammatory diseases of the eye, including corneal dystrophy, trachoma, onchocerciasis, uveitis, sympathetic ophthalmitis and endophthalmitis; chronic inflammatory diseases of the gum, including gingivitis and periodontitis; tuberculosis; leprosy; inflammatory diseases of the kidney, including uremic complications, glomerulonephritis and nephrosis; inflammatory diseases of the skin, including sclerodermatitis, psoriasis and eczema; inflammatory diseases of the central nervous system, including chronic demyelinating diseases of the nervous system, multiple sclerosis, AIDS-related neurodegeneration and Alzheimer s disease, infectious meningitis, encephalomyelitis, Parkinson's disease, Huntington's disease, amyotrophic lateral sclerosis and viral or autoimmune encephalitis; autoimmune diseases, including Type I and Type II diabetes mellitus; diabetic complications, including, but not limited to, diabetic cataract, glaucoma, retinopathy, nephropathy (such as microaluminuria and progressive diabetic nephropathy), polyneuropathy, mononeuropathies, autonomic neuropathy, gangrene of the feet,

atherosclerotic coronary arterial disease, peripheral arterial disease, nonketotic hyperglycemic-hyperosmolar coma, foot ulcers, joint problems, and a skin or mucous membrane complication (such as an infection, a shin spot, a candidal infection or necrobiosis lipoidica diabeticorum); immune-complex vasculitis, and systemic lupus erythematosus (SLE); inflammatory diseases of the heart, such as cardiomyopathy, ischemic heart disease hypercholesterolemia, and atherosclerosis; as well as various other diseases that can have significant inflammatory components, including preeclampsia, chronic liver failure, brain and spinal cord trauma, and cancer. The Cyanoiminopiperazine Compounds can also be used for inhibiting, treating, or preventing pain associated with inflammatory disease that can, for example, be a systemic inflammation of the body, exemplified by gram-positive or gram negative shock, hemorrhagic or anaphylactic shock, or shock induced by cancer chemotherapy in response to pro-inflammatory cytokines, e.g., shock associated with pro-inflammatory cytokines. Such shock can be induced, e.g., by a chemotherapeutic agent that is adminstered as a treatment for cancer.

The Cyanoiminopiperazine Compounds can be used to treat or prevent UI. Examples of UI treatable or preventable using the Cyanoiminopiperazine Compounds include, but are not limited to, urge incontinence, stress incontinence, overflow incontinence, neurogenic incontinence, and total incontinence.

The Cyanoiminopiperazine Compounds can be used to treat or prevent an ulcer. Examples of ulcers treatable or preventable using the Cyanoiminopiperazine Compounds include, but are not limited to, a duodenal ulcer, a gastric ulcer, a marginal ulcer, an esophageal ulcer, or a stress ulcer.

The Cyanoiminopiperazine Compounds can be used to treat or prevent IBD, including Crohn's disease and ulcerative colitis.

The Cyanoiminopiperazine Compounds can be used to treat or prevent IBS. Examples of IBS treatable or preventable using the Cyanoiminopiperazine Compounds include, but are not limited to, spastic-colon-type IBS and constipation-predominant IBS.

The Cyanoiminopiperazine Compounds can be used to treat or prevent an addictive disorder, including but not limited to, an eating disorder, an impulse-control disorder, an alcohol-related disorder, a nicotine-related disorder, an amphetamine-related disorder, a cannabis-related disorder, a cocaine-related disorder, an hallucinogen-related

disorder, an inhalant-related disorders, and an opioid-related disorder, all of which are further sub-classified as listed below.

Eating disorders include, but are not limited to, Bulimia Nervosa, Nonpurging Type; Bulimia Nervosa, Purging Type; Anorexia; and Eating Disorder not otherwise specified (NOS).

Impulse control disorders include, but are not limited to, Intermittent Explosive Disorder, Kleptomania, Pyromania, Pathological Gambling, Trichotillomania, and Impulse Control Disorder not otherwise specified (NOS).

Alcohol-related disorders include, but are not limited to, Alcohol-Induced Psychotic Disorder with delusions, Alcohol Abuse, Alcohol Intoxication, Alcohol Withdrawal, Alcohol Intoxication Delirium, Alcohol Withdrawal Delirium, Alcohol-Induced Persisting Dementia, Alcohol-Induced Persisting Amnestic Disorder, Alcohol Dependence, Alcohol-Induced Psychotic Disorder with hallucinations, Alcohol-Induced Mood Disorder, Alcohol-Induced Anxiety Disorder, Alcohol-Induced Sexual Dysfunction, Alcohol-Induced Sleep Disorder, Alcohol-Related Disorder not otherwise specified (NOS), Alcohol Intoxication, and Alcohol Withdrawal.

Nicotine-related disorders include, but are not limited to, Nicotine Dependence, Nicotine Withdrawal, and Nicotine-Related Disorder not otherwise specified (NOS).

Amphetamine-related disorders include, but are not limited to, Amphetamine Dependence, Amphetamine Abuse, Amphetamine Intoxication, Amphetamine Withdrawal, Amphetamine Intoxication Delirium, Amphetamine-Induced Psychotic Disorder with delusions, Amphetamine-Induced Psychotic Disorders with hallucinations, Amphetamine-Induced Mood Disorder, Amphetamine-Induced Anxiety Disorder, Amphetamine-Induced Sexual Dysfunction, Amphetamine-Induced Sleep Disorder, Amphetamine Related Disorder not otherwise specified (NOS), Amphetamine Intoxication, and Amphetamine Withdrawal.

Cannabis-related disorders include, but are not limited to, Cannabis Dependence, Cannabis Abuse, Cannabis Intoxication, Cannabis Intoxication Delirium, Cannabis-Induced Psychotic Disorder with delusions, Cannabis-Induced Psychotic Disorder

with hallucinations, Cannabis-Induced Anxiety Disorder, Cannabis Related Disorder not otherwise specified (NOS), and Cannabis Intoxication.

Cocaine-related disorders include, but are not limited to, Cocaine Dependence, Cocaine Abuse, Cocaine Intoxication, Cocaine Withdrawal, Cocaine Intoxication Delirium, Cocaine-Induced Psychotic Disorder with delusions, Cocaine-Induced Psychotic Disorders with hallucinations, Cocaine-Induced Mood Disorder, Cocaine-Induced Anxiety Disorder, Cocaine-Induced Sexual Dysfunction, Cocaine-Induced Sleep Disorder, Cocaine Related Disorder not otherwise specified (NOS), Cocaine Intoxication, and Cocaine Withdrawal.

Hallucinogen-related disorders include, but are not limited to, Hallucinogen Dependence, Hallucinogen Abuse, Hallucinogen Intoxication, Hallucinogen Withdrawal, Hallucinogen Intoxication Delirium, Hallucinogen-Induced Psychotic Disorder with delusions, Hallucinogen-Induced Psychotic Disorders with hallucinations, Hallucinogen-Induced Mood Disorder, Hallucinogen-Induced Anxiety Disorder, Hallucinogen-Induced Sexual Dysfunction, Hallucinogen-Induced Sleep Disorder, Hallucinogen Related Disorder not otherwise specified (NOS), Hallucinogen Intoxication, and Hallucinogen Persisting Perception Disorder (Flashbacks).

Inhalant-related disorders include, but are not limited to, Inhalant Dependence, Inhalant Abuse, Inhalant Intoxication, Inhalant Intoxication Delirium, Inhalant-Induced Psychotic Disorder with delusions, Inhalant-Induced Psychotic Disorder with hallucinations, Inhalant-Induced Anxiety Disorder, Inhalant Related Disorder not otherwise specified (NOS), and Inhalant Intoxication.

Opioid-related disorders include, but are not limited to, Opioid Dependence, Opioid Abuse, Opioid Intoxication, Opioid Intoxication Delirium, Opioid-Induced Psychotic Disorder with delusions, Opioid-Induced Psychotic Disorder with hallucinations, Opioid-Induced Anxiety Disorder, Opioid Related Disorder not otherwise specified (NOS), Opioid Intoxication, and Opioid Withdrawal.

The Cyanoiminopiperazine Compounds can be used to treat or prevent Parkinson's disease and parkinsonism and the symptoms associated with Parkinson's disease and parkinsonism, including but not limited to, bradykinesia, muscular rigidity, resting tremor, and impairment of postural balance.

The Cyanoiminopiperazine Compounds can be used to treat or prevent generalized anxiety or severe anxiety and the symptoms associated with anxiety, including but not limited to, restlessness; tension; tachycardia; dyspnea; depression, including chronic "neurotic" depression; panic disorder; agoraphobia and other specific phobias; eating disorders; and personality disorders.

The Cyanoiminopiperazine Compounds can be used to treat or prevent epilepsy, including but not limited to, partial epilepsy, generalized epilepsy, and the symptoms associated with epilepsy, including but not limited to, simple partial seizures, jacksonian seizures, complex partial (psychomotor) seizures, convulsive seizures (grand mal or tonic-clonic seizures), petit mal (absence) seizures, and status epilepticus.

The Cyanoiminopiperazine Compounds can be used to treat or prevent strokes, including but not limited to, ischemic strokes and hemorrhagic strokes.

The Cyanoiminopiperazine Compounds can be used to treat or prevent a seizure, including but not limited to, infantile spasms, febrile seizures, and epileptic seizures.

The Cyanoiminopiperazine Compounds can be used to treat or prevent a pruritic condition, including but not limited to, pruritus caused by dry skin, scabies, dermatitis, herpetiformis, atopic dermatitis, *pruritus vulvae et ani*, miliaria, insect bites, pediculosis, contact dermatitis, drug reactions, urticaria, urticarial eruptions of pregnancy, psoriasis, lichen planus, lichen simplex chronicus, exfoliative dermatitis, folliculitis, bullous pemphigoid, or fiberglass dermatitis.

The Cyanoiminopiperazine Compounds can be used to treat or prevent psychosis, including but not limited to, schizophrenia, including paranoid schizophrenia, hebephrenic or disorganized schizophrenia, catatonic schizophrenia, undifferentiated schizophrenia, negative or deficit subtype schizophrenia, and non-deficit schizophrenia; a delusional disorder, including erotomanic subtype delusional disorder, grandiose subtype delusional disorder, jealous subtype delusional disorder, persecutory subtype delusional disorder, and somatic subtype delusional disorder; and brief psychosis.

The Cyanoiminopiperazine Compounds can be used to treat or prevent a cognitive disorder, including but not limited to, delirium and dementia such as multi-infarct dementia, dementia pugilistica, dimentia caused by AIDS, and dementia caused by Alzheimer's disease.

The Cyanoiminopiperazine Compounds can be used to treat or prevent a memory deficiency, including but not limited to, dissociative amnesia and dissociative fugue.

The Cyanoiminopiperazine Compounds can be used to treat or prevent restricted brain function, including but not limited to, that caused by surgery or an organ transplant, restricted blood supply to the brain, a spinal cord injury, a head injury, hypoxia, cardiac arrest, or hypoglycemia.

The Cyanoiminopiperazine Compounds can be used to treat or prevent Huntington's chorea.

The Cyanoiminopiperazine Compounds can be used to treat or prevent ALS.

The Cyanoiminopiperazine Compounds can be used to treat or prevent retinopathy, including but not limited to, arteriosclerotic retinopathy, diabetic arteriosclerotic retinopathy, hypertensive retinopathy, non-proliferative retinopathy, and proliferative retinopathy.

The Cyanoiminopiperazine Compounds can be used to treat or prevent a muscle spasm.

The Cyanoiminopiperazine Compounds can be used to treat or prevent a migraine.

The Cyanoiminopiperazine Compounds can be used to inhibit, treat or prevent vomiting, including but not limited to, nausea vomiting, dry vomiting (retching), and regurgitation.

The Cyanoiminopiperazine Compounds can be used to treat or prevent dyskinesia, including but not limited to, tardive dyskinesia and biliary dyskinesia.

The Cyanoiminopiperazine Compounds can be used to treat or prevent depression, including but not limited to, major depression and bipolar disorder.

Applicants believe that the Cyanoiminopiperazine Compounds are antagonists for VR1.

The invention also relates to methods for inhibiting VR1 function in a cell, comprising contacting a cell capable of expressing VR1 with an effective amount of a Cyanoiminopiperazine Compound. This method can be used *in vitro*, for example, as an assay to select cells that express VR1 and, accordingly, are useful as part of an assay to select compounds useful for treating or preventing pain, UI, an ulcer, IBD, or IBS. The method is

also useful for inhibiting VR1 function in a cell *in vivo*, in an animal, a human in one embodiment, by contacting a cell, in an animal, with an effective amount of a Cyanoiminopiperazine Compound. In one embodiment, the method is useful for treating or preventing pain in an animal. In another embodiment, the method is useful for treating or preventing UI in an animal. In another embodiment, the method is useful for treating or preventing an ulcer in an animal. In another embodiment, the method is useful for treating or preventing IBD in an animal. In another embodiment, the method is useful for treating or preventing IBS in an animal.

Examples of tissue comprising cells capable of expressing VR1 include, but are not limited to, neuronal, brain, kidney, urothelium, and bladder tissue. Methods for assaying cells that express VR1 are well known in the art.

Applicants believe that the Cyanoiminopiperazine Compounds are antagonists for mGluR5.

The invention also relates to methods for inhibiting mGluR5 function in a cell, comprising contacting a cell capable of expressing mGluR5 with an amount of a Cyanoiminopiperazine Compound effective to inhibit mGluR5 function in the cell. This method can be used *in vitro*, for example, as an assay to select cells that express mGluR5 and, accordingly, are useful as part of an assay to select compounds useful for treating or preventing pain, an addictive disorder, Parkinson's disease, parkinsonism, anxiety, a pruritic condition, or psychosis. The method is also useful for inhibiting mGluR5 function in a cell *in vivo*, in an animal, a human in one embodiment, by contacting a cell, in an animal, with an amount of a Cyanoiminopiperazine Compound effective to inhibit mGluR5 function in the cell. In one embodiment, the method is useful for treating or preventing pain in an animal in need thereof. In another embodiment, the method is useful for treating or preventing an addictive disorder in an animal in need thereof. In another embodiment, the method is useful for treating or preventing Parkinson's disease in an animal in need thereof. In another embodiment, the method is useful for treating or preventing parkinsonism in an animal in need thereof. In another embodiment, the method is useful for treating or preventing anxiety in an animal in need thereof. In another embodiment, the method is useful for treating or preventing a pruritic condition in an animal in need thereof. In another embodiment, the method is useful for treating or preventing psychosis in an animal in need thereof.

Examples of cells capable of expressing mGluR5 are neuronal and glial cells of the central nervous system, particularly the brain, especially in the nucleus accumbens. Methods for assaying cells that express mGluR5 are well known in the art.

Applicants believe that the Cyanoiminopiperazine Compounds are antagonists for mGluR1.

The invention also relates to methods for inhibiting mGluR1 function in a cell, comprising contacting a cell capable of expressing mGluR1 with an amount of a Cyanoiminopiperazine Compound effective to inhibit mGluR1 function in the cell. This method can be used *in vitro*, for example, as an assay to select cells that express mGluR1 and, accordingly, are useful as part of an assay to select compounds useful for treating or preventing pain, UI, an addictive disorder, Parkinson's disease, parkinsonism, anxiety, epilepsy, stroke, a seizure, a pruritic condition, psychosis, a cognitive disorder, a memory deficit, restricted brain function, Huntington's chorea, ALS, dementia, retinopathy, a muscle spasm, a migraine, vomiting, dyskinesia, or depression. The method is also useful for inhibiting mGluR1 function in a cell *in vivo*, in an animal, a human in one embodiment, by contacting a cell, in an animal, with an amount of a Cyanoiminopiperazine Compound effective to inhibit mGluR1 function in the cell. In one embodiment, the method is useful for treating or preventing pain in an animal in need thereof. In another embodiment, the method is useful for treating or preventing UI in an animal in need thereof. In another embodiment, the method is useful for treating or preventing an addictive disorder in an animal in need thereof. In another embodiment, the method is useful for treating or preventing Parkinson's disease in an animal in need thereof. In another embodiment, the method is useful for treating or preventing parkinsonism in an animal in need thereof. In another embodiment, the method is useful for treating or preventing anxiety in an animal in need thereof. In another embodiment, the method is useful for treating or preventing epilepsy in an animal in need thereof. In another embodiment, the method is useful for treating or preventing stroke in an animal in need thereof. In another embodiment, the method is useful for treating or preventing a seizure in an animal in need thereof. In another embodiment, the method is useful for treating or preventing a pruritic condition in an animal in need thereof. In another embodiment, the method is useful for treating or preventing psychosis in an animal in need thereof. In another embodiment, the method is useful for treating or preventing a cognitive

disorder in an animal in need thereof. In another embodiment, the method is useful for treating or preventing a memory deficit in an animal in need thereof. In another embodiment, the method is useful for treating or preventing restricted brain function in an animal in need thereof. In another embodiment, the method is useful for treating or preventing Huntington's chorea in an animal in need thereof. In another embodiment, the method is useful for treating or preventing ALS in an animal in need thereof. In another embodiment, the method is useful for treating or preventing dementia in an animal in need thereof. In another embodiment, the method is useful for treating or preventing retinopathy in an animal in need thereof. In another embodiment, the method is useful for treating or preventing a muscle spasm in an animal in need thereof. In another embodiment, the method is useful for treating or preventing a migraine in an animal in need thereof. In another embodiment, the method is useful for treating or preventing vomiting in an animal in need thereof. In another embodiment, the method is useful for treating or preventing dyskinesia in an animal in need thereof. In another embodiment, the method is useful for treating or preventing depression in an animal in need thereof.

Examples of cells capable of expressing mGluR1 include, but are not limited to, cerebellar Purkinje neuron cells, Purkinje cell bodies (punctate), cells of spine(s) of the cerebellum; neurons and neurophil cells of olfactory-bulb glomeruli; cells of the superficial layer of the cerebral cortex; hippocampus cells; thalamus cells; superior colliculus cells; and spinal trigeminal nucleus cells. Methods for assaying cells that express mGluR1 are well known in the art.

4.19.1 THERAPEUTIC/PROPHYLACTIC ADMINISTRATION AND COMPOSITIONS OF THE INVENTION

Due to their activity, the Cyanoiminopiperazine Compounds are advantageously useful in veterinary and human medicine. As described above, the Cyanoiminopiperazine Compounds are useful for treating or preventing pain, UI, an ulcer, IBD, IBS, an addictive disorder, Parkinson's disease, parkinsonism, anxiety, epilepsy, stroke, a seizure, a pruritic condition, psychosis, a cognitive disorder, a memory deficit, restricted brain function, Huntington's chorea, ALS, dementia, retinopathy, a muscle spasm, a migraine, vomiting, dyskinesia, or depression in an animal in need thereof.

When administered to an animal, the Cyanoiminopiperazine Compounds are administered as a component of a composition that comprises a pharmaceutically acceptable carrier or excipient. The present compositions, which comprise a Cyanoiminopiperazine Compound, can be administered orally. The Cyanoiminopiperazine Compounds of the invention can also be administered by any other convenient route, for example, by infusion or bolus injection, by absorption through epithelial or mucocutaneous linings (*e.g.*, oral, rectal, and intestinal mucosa, *etc.*) and can be administered together with another biologically active agent. Administration can be systemic or local. Various delivery systems are known, *e.g.*, encapsulation in liposomes, microparticles, microcapsules, capsules, *etc.*, and can be used to administer the Cyanoiminopiperazine Compound.

Methods of administration include, but are not limited to, intradermal, intramuscular, intraperitoneal, intravenous, subcutaneous, intranasal, epidural, oral, sublingual, intracerebral, intravaginal, transdermal, rectal, by inhalation, or topical, particularly to the ears, nose, eyes, or skin. The mode of administration is left to the discretion of the practitioner. In most instances, administration will result in the release of the Cyanoiminopiperazine Compounds into the bloodstream.

In specific embodiments, it can be desirable to administer the Cyanoiminopiperazine Compounds locally. This can be achieved, for example, and not by way of limitation, by local infusion during surgery, topical application, *e.g.*, in conjunction with a wound dressing after surgery, by injection, by means of a catheter, by means of a suppository or enema, or by means of an implant, said implant being of a porous, non-porous, or gelatinous material, including membranes, such as sialastic membranes, or fibers.

In certain embodiments, it can be desirable to introduce the Cyanoiminopiperazine Compounds into the central nervous system or gastrointestinal tract by any suitable route, including intraventricular, intrathecal, and epidural injection, and enema. Intraventricular injection can be facilitated by an intraventricular catheter, for example, attached to a reservoir, such as an Ommaya reservoir.

Pulmonary administration can also be employed, *e.g.*, by use of an inhaler or nebulizer, and formulation with an aerosolizing agent, or via perfusion in a fluorocarbon or synthetic pulmonary surfactant. In certain embodiments, the Cyanoiminopiperazine

Compounds can be formulated as a suppository, with traditional binders and excipients such as triglycerides.

In another embodiment, the Cyanoiminopiperazine Compounds can be delivered in a vesicle, in particular a liposome (*see* Langer, *Science* 249:1527-1533 (1990) and Treat *et al.*, *Liposomes in the Therapy of Infectious Disease and Cancer* 317-327 and 353-365 (1989)).

In yet another embodiment, the Cyanoiminopiperazine Compounds can be delivered in a controlled-release system or sustained-release system (*see*, *e.g.*, Goodson, in Medical Applications of Controlled Release, *supra*, vol. 2, pp. 115-138 (1984)). Other controlled- or sustained-release systems discussed in the review by Langer, *Science* 249:1527-1533 (1990) can be used. In one embodiment, a pump can be used (Langer, *Science* 249:1527-1533 (1990); Sefton, *CRC Crit. Ref. Biomed. Eng.* 14:201 (1987); Buchwald *et al.*, *Surgery* 88:507 (1980); and Saudek *et al.*, *N. Engl. J. Med.* 321:574 (1989)). In another embodiment, polymeric materials can be used (*see Medical Applications of Controlled Release* (Langer and Wise eds., 1974); *Controlled Drug Bioavailability, Drug Product Design and Performance* (Smolen and Ball eds., 1984); Ranger and Peppas, *J. Macromol. Sci. Rev. Macromol. Chem.* 23:61 (1983); Levy *et al.*, *Science* 228:190 (1985); During *et al.*, *Ann. Neurol.* 25:351 (1989); and Howard *et al.*, *J. Neurosurg.* 71:105 (1989)). In yet another embodiment, a controlled- or sustained-release system can be placed in proximity of a target of the Cyanoiminopiperazine Compounds, *e.g.*, the spinal column, brain, or gastrointestinal tract, thus requiring only a fraction of the systemic dose.

The present compositions can optionally comprise a suitable amount of a pharmaceutically acceptable excipient so as to provide the form for proper administration to the animal.

Such pharmaceutical excipients can be liquids, such as water and oils, including those of petroleum, animal, vegetable, or synthetic origin, such as peanut oil, soybean oil, mineral oil, sesame oil and the like. The pharmaceutical excipients can be saline, gum acacia, gelatin, starch paste, talc, keratin, colloidal silica, urea and the like. In addition, auxiliary, stabilizing, thickening, lubricating, and coloring agents can be used. In one embodiment, the pharmaceutically acceptable excipients are sterile when administered to an animal. Water is a particularly useful excipient when the Cyanoiminopiperazine

Compound is administered intravenously. Saline solutions and aqueous dextrose and glycerol solutions can also be employed as liquid excipients, particularly for injectable solutions. Suitable pharmaceutical excipients also include starch, glucose, lactose, sucrose, gelatin, malt, rice, flour, chalk, silica gel, sodium stearate, glycerol monostearate, talc, sodium chloride, dried skim milk, glycerol, propylene, glycol, water, ethanol and the like. The present compositions, if desired, can also contain minor amounts of wetting or emulsifying agents, or pH buffering agents.

The present compositions can take the form of solutions, suspensions, emulsion, tablets, pills, pellets, capsules, capsules containing liquids, powders, sustained-release formulations, suppositories, emulsions, aerosols, sprays, suspensions, or any other form suitable for use. In one embodiment, the composition is in the form of a capsule (see *e.g.*, U.S. Patent No. 5,698,155). Other examples of suitable pharmaceutical excipients are described in *Remington's Pharmaceutical Sciences* 1447-1676 (Alfonso R. Gennaro ed., 19th ed. 1995), incorporated herein by reference.

In one embodiment, the Cyanoiminopiperazine Compounds are formulated in accordance with routine procedures as a composition adapted for oral administration to human beings. Compositions for oral delivery can be in the form of tablets, lozenges, aqueous or oily suspensions, granules, powders, emulsions, capsules, syrups, or elixirs, for example. Orally administered compositions can contain one or more agents, for example, sweetening agents such as fructose, aspartame or saccharin; flavoring agents such as peppermint, oil of wintergreen, or cherry; coloring agents; and preserving agents, to provide a pharmaceutically palatable preparation. Moreover, where in tablet or pill form, the compositions can be coated to delay disintegration and absorption in the gastrointestinal tract thereby providing a sustained action over an extended period of time. Selectively permeable membranes surrounding an osmotically active driving compound are also suitable for orally administered compositions. In these latter platforms, fluid from the environment surrounding the capsule is imbibed by the driving compound, which swells to displace the agent or agent composition through an aperture. These delivery platforms can provide an essentially zero order delivery profile as opposed to the spiked profiles of immediate release formulations. A time-delay material such as glycerol monostearate or glycerol stearate can also be used. Oral compositions can include standard excipients such as mannitol, lactose, starch, magnesium

stearate, sodium saccharin, cellulose, and magnesium carbonate. In one embodiment, the excipients are of pharmaceutical grade.

In another embodiment, the Cyanoiminopiperazine Compounds can be formulated for intravenous administration. Typically, compositions for intravenous administration comprise sterile isotonic aqueous buffer. Where necessary, the compositions can also include a solubilizing agent. Compositions for intravenous administration can optionally include a local anesthetic such as lignocaine to lessen pain at the site of the injection. Generally, the ingredients are supplied either separately or mixed together in unit dosage form, for example, as a dry lyophilized powder or water free concentrate in a hermetically sealed container such as an ampule or sachette indicating the quantity of active agent. Where the Cyanoiminopiperazine Compounds are to be administered by infusion, they can be dispensed, for example, with an infusion bottle containing sterile pharmaceutical grade water or saline. Where the Cyanoiminopiperazine Compounds are administered by injection, an ampule of sterile water for injection or saline can be provided so that the ingredients can be mixed prior to administration.

The Cyanoiminopiperazine Compounds can be administered by controlled-release or sustained-release means or by delivery devices that are well known to those of ordinary skill in the art. Examples include, but are not limited to, those described in U.S. Patent Nos.: 3,845,770; 3,916,899; 3,536,809; 3,598,123; 4,008,719; 5,674,533; 5,059,595; 5,591,767; 5,120,548; 5,073,543; 5,639,476; 5,354,556; and 5,733,566, each of which is incorporated herein by reference. Such dosage forms can be used to provide controlled- or sustained-release of one or more active ingredients using, for example, hydropropylmethyl cellulose, other polymer matrices, gels, permeable membranes, osmotic systems, multilayer coatings, microparticles, liposomes, microspheres, or a combination thereof to provide the desired release profile in varying proportions. Suitable controlled- or sustained-release formulations known to those of ordinary skill in the art, including those described herein, can be readily selected for use with the active ingredients of the invention. The invention thus encompasses single unit dosage forms suitable for oral administration such as, but not limited to, tablets, capsules, gelcaps, and caplets that are adapted for controlled- or sustained-release.

Controlled- or sustained-release pharmaceutical compositions can have a common goal of improving drug therapy over that achieved by their non-controlled or non-

sustained counterparts. In one embodiment, a controlled- or sustained-release composition comprises a minimal amount of a Cyanoiminopiperazine Compound to cure or control the condition in a minimum amount of time. Advantages of controlled- or sustained-release compositions include extended activity of the drug, reduced dosage frequency, and increased patient compliance. In addition, controlled- or sustained-release compositions can favorably affect the time of onset of action or other characteristics, such as blood levels of the Cyanoiminopiperazine Compound, and can thus reduce the occurrence of adverse side effects.

Controlled- or sustained-release compositions can initially release an amount of a Cyanoiminopiperazine Compound that promptly produces the desired therapeutic or prophylactic effect, and gradually and continually release other amounts of the Cyanoiminopiperazine Compound to maintain this level of therapeutic or prophylactic effect over an extended period of time. To maintain a constant level of the Cyanoiminopiperazine Compound in the body, the Cyanoiminopiperazine Compound can be released from the dosage form at a rate that will replace the amount of Cyanoiminopiperazine Compound being metabolized and excreted from the body. Controlled- or sustained-release of an active ingredient can be stimulated by various conditions, including but not limited to, changes in pH, changes in temperature, concentration or availability of enzymes, concentration or availability of water, or other physiological conditions or compounds.

The amount of the Cyanoiminopiperazine Compound that is effective in the treatment or prevention of pain, UI, an ulcer, IBD, IBS, an addictive disorder, Parkinson's disease, parkinsonism, anxiety, epilepsy, stroke, a seizure, a pruritic condition, psychosis, a cognitive disorder, a memory deficit, restricted brain function, Huntington's chorea, ALS, dementia, retinopathy, a muscle spasm, a migraine, vomiting, dyskinesia, or depression and can be determined by standard clinical techniques. In addition, *in vitro* or *in vivo* assays can optionally be employed to help identify optimal dosage ranges. The precise dose to be employed will also depend on the route of administration, and the seriousness of the condition being treated and should be decided according to the judgment of the practitioner and each patient's circumstances in view of, *e.g.*, published clinical studies. Suitable effective dosage amounts, however, range from about 10 micrograms to about 2500 milligrams about every 4 h, although they are typically about 100 mg or less. In one embodiment, the effective

dosage amount ranges from about 0.01 milligrams to about 100 milligrams of a Cyanoiminopiperazine Compound about every 4 h, in another embodiment, about 0.020 milligrams to about 50 milligrams about every 4 h, and in another embodiment, about 0.025 milligrams to about 20 milligrams about every 4 h. The effective dosage amounts described herein refer to total amounts administered; that is, if more than one Cyanoiminopiperazine Compound is administered, the effective dosage amounts correspond to the total amount administered.

Where a cell capable of expressing VR1, mGluR5, or mGluR1 is contacted with a Cyanoiminopiperazine Compound *in vitro*, the amount effective for inhibiting the receptor function in a cell will typically range from about 0.01 μg/L to about 5 mg/L, in one embodiment, from about 0.01 μg/L to about 2.5 mg/L, in another embodiment, from about 0.01 μg/L to about 0.5 mg/L, and in another embodiment, from about 0.01 μg/L to about 0.25 mg/L of a solution or suspension of a pharmaceutically acceptable carrier or excipient. In one embodiment, the volume of solution or suspension is from about 1 μL to about 1 mL. In another embodiment, the volume of solution or suspension is about 200 μL.

Where a cell capable of expressing VR1, mGluR5, or mGluR1 is contacted with a Cyanoiminopiperazine Compound *in vivo*, the amount effective for inhibiting the receptor function in a cell will typically range from about 0.01 mg to about 100 mg/kg of body weight per day, in one embodiment, from about 0.1 mg to about 50 mg/kg body weight per day, and in another embodiment, from about 1 mg to about 20 mg/kg of body weight per day.

The Cyanoiminopiperazine Compounds can be assayed *in vitro* or *in vivo* for the desired therapeutic or prophylactic activity prior to use in humans. Animal model systems can be used to demonstrate safety and efficacy.

The present methods for treating or preventing pain, UI, an ulcer, IBD, IBS, an addictive disorder, Parkinson's disease, parkinsonism, anxiety, epilepsy, stroke, a seizure, a pruritic condition, psychosis, a cognitive disorder, a memory deficit, restricted brain function, Huntington's chorea, ALS, dementia, retinopathy, a muscle spasm, a migraine, vomiting, dyskinesia, or depression in an animal in need thereof can further comprise administering to the animal being administered a Cyanoiminopiperazine Compound another therapeutic agent. In one embodiment, the other therapeutic agent is administered in an effective amount.

The present methods for inhibiting VR1 function in a cell capable of expressing VR1 can further comprise contacting the cell with an effective amount of another therapeutic agent.

The present methods for inhibiting mGluR5 function in a cell capable of expressing mGluR5 can further comprise contacting the cell with an effective amount of another therapeutic agent.

The present methods for inhibiting mGluR1 function in a cell capable of expressing mGluR1 can further comprise contacting the cell with an effective amount of another therapeutic agent.

The other therapeutic agent includes, but is not limited to, an opioid agonist, a non-opioid analgesic, a non-steroid anti-inflammatory agent, an antimigraine agent, a Cox-II inhibitor, an antiemetic, a β-adrenergic blocker, an anticonvulsant, an antidepressant, a Ca2+-channel blocker, an anticancer agent, an agent for treating or preventing UI, an agent for treating or preventing an ulcer, an agent for treating or preventing IBD, an agent for treating or preventing IBS, an agent for treating addictive disorder, an agent for treating Parkinson's disease and parkinsonism, an agent for treating anxiety, an agent for treating epilepsy, an agent for treating a stroke, an agent for treating a seizure, an agent for treating a pruritic condition, an agent for treating psychosis, an agent for treating Huntington's chorea, an agent for treating ALS, an agent for treating a cognitive disorder, an agent for treating a migraine, an agent for treating vomiting, an agent for treating dyskinesia, or an agent for treating depression, and mixtures thereof.

Effective amounts of the other therapeutic agents are well known to those skilled in the art. However, it is well within the skilled artisan's purview to determine the other therapeutic agent's optimal effective-amount range. In one embodiment of the invention, where another therapeutic agent is administered to an animal, the effective amount of the Cyanoiminopiperazine Compound is less than its effective amount would be where the other therapeutic agent is not administered. In this case, without being bound by theory, it is believed that the Cyanoiminopiperazine Compounds and the other therapeutic agent act synergistically to treat or prevent pain, UI, an ulcer, IBD, IBS, an addictive disorder, Parkinson's disease, parkinsonism, anxiety, epilepsy, stroke, a seizure, a pruritic condition, psychosis, a cognitive disorder, a memory deficit, restricted brain function, Huntington's

chorea, ALS, dementia, retinopathy, a muscle spasm, a migraine, vomiting, dyskinesia, or depression.

Examples of useful opioid agonists include, but are not limited to, alfentanil, allylprodine, alphaprodine, anileridine, benzylmorphine, bezitramide, buprenorphine, butorphanol, clonitazene, codeine, desomorphine, dextromoramide, dezocine, diampromide, diamorphone, dihydrocodeine, dihydromorphine, dimenoxadol, dimepheptanol, dimethylthiambutene, dioxaphetyl butyrate, dipipanone, eptazocine, ethoheptazine, ethylmethylthiambutene, ethylmorphine, etonitazene fentanyl, heroin, hydrocodone, hydromorphone, hydroxypethidine, isomethadone, ketobemidone, levorphanol, levophenacylmorphan, lofentanil, meperidine, meptazinol, metazocine, methadone, metopon, morphine, myrophine, nalbuphine, narceine, nicomorphine, norlevorphanol, normethadone, nalorphine, normorphine, norpipanone, opium, oxycodone, oxymorphone, papaveretum, pentazocine, phenadoxone, phenomorphan, phenazocine, phenoperidine, piminodine, piritramide, proheptazine, promedol, properidine, propiram, propoxyphene, sufentanil, tilidine, tramadol, pharmaceutically acceptable salts thereof, and mixtures thereof.

In certain embodiments, the opioid agonist is selected from codeine, hydromorphone, hydrocodone, oxycodone, dihydrocodeine, dihydromorphine, morphine, tramadol, oxymorphone, pharmaceutically acceptable salts thereof, and mixtures thereof.

Examples of useful non-opioid analgesics include non-steroidal anti-inflammatory agents, such as aspirin, ibuprofen, diclofenac, naproxen, benoxaprofen, flurbiprofen, fenoprofen, flubufen, ketoprofen, indoprofen, piroprofen, carprofen, oxaprozin, pramoprofen, muroprofen, trioxaprofen, suprofen, aminoprofen, tiaprofenic acid, fluprofen, bucloxic acid, indomethacin, sulindac, tolmetin, zomepirac, tiopinac, zidometacin, acemetacin, fentiazac, clidanac, oxpinac, mefenamic acid, meclofenamic acid, flufenamic acid, niflumic acid, tolfenamic acid, diflurisal, flufenisal, piroxicam, sudoxicam, isoxicam, and pharmaceutically acceptable salts thereof, and mixtures thereof. Other suitable non-opioid analgesics include the following, non-limiting, chemical classes of analgesic, antipyretic, nonsteroidal anti-inflammatory drugs: salicylic acid derivatives, including aspirin, sodium salicylate, choline magnesium trisalicylate, salsalate, diflunisal, salicylsalicylic acid, sulfasalazine, and olsalazin; para-aminophennol derivatives including

acetaminophen and phenacetin; indole and indene acetic acids, including indomethacin, sulindac, and etodolac; heteroaryl acetic acids, including tolmetin, diclofenac, and ketorolac; anthranilic acids (fenamates), including mefenamic acid and meclofenamic acid; enolic acids, including oxicams (piroxicam, tenoxicam), and pyrazolidinediones (phenylbutazone, oxyphenthartazone); and alkanones, including nabumetone. For a more detailed description of the NSAIDs, *see Paul A. Insel, Analgesic-Antipyretic and Anti-inflammatory Agents and Drugs Employed in the Treatment of Gout, in Goodman & Gilman's The Pharmacological Basis of Therapeutics* 617-57 (Perry B. Molinhoff and Raymond W. Ruddon eds., 9th ed 1996) and Glen R. Hanson, *Analgesic, Antipyretic and Anti-Inflammatory Drugs in Remington: The Science and Practice of Pharmacy Vol II* 1196-1221 (A.R. Gennaro ed. 19th ed. 1995) which are hereby incorporated by reference in their entireties.

Examples of useful Cox-II inhibitors and 5-lipoxygenase inhibitors, as well as combinations thereof, are described in U.S. Patent No. 6,136,839, which is hereby incorporated by reference in its entirety. Examples of useful Cox-II inhibitors include, but are not limited to, rofecoxib and celecoxib.

Examples of useful antimigraine agents include, but are not limited to, alpiropride, dihydroergotamine, dolasetron, ergocornine, ergocorninine, ergocryptine, ergot, ergotamine, flumedroxone acetate, fonazine, lisuride, lomerizine, methysergide oxetorone, pizotyline, and mixtures thereof.

The other therapeutic agent can also be an agent useful for reducing any potential side effects of a Cyanoiminopiperazine Compounds. For example, the other therapeutic agent can be an antiemetic agent. Examples of useful antiemetic agents include, but are not limited to, metoclopromide, domperidone, prochlorperazine, promethazine, chlorpromazine, trimethobenzamide, ondansetron, granisetron, hydroxyzine, acetylleucine monoethanolamine, alizapride, azasetron, benzquinamide, bietanautine, bromopride, buclizine, clebopride, cyclizine, dimenhydrinate, diphenidol, dolasetron, meclizine, methallatal, metopimazine, nabilone, oxyperndyl, pipamazine, scopolamine, sulpiride, tetrahydrocannabinol, thiethylperazine, thioproperazine, tropisetron, and mixtures thereof.

Examples of useful β-adrenergic blockers include, but are not limited to, acebutolol, alprenolol, amosulabol, arotinolol, atenolol, befunolol, betaxolol, bevantolol, bisoprolol, bopindolol, bucumolol, bufetolol, bufuralol, bunitrolol, bupranolol, butidrine

hydrochloride, butofilolol, carazolol, carteolol, carvedilol, celiprolol, cetamolol, cloranolol, dilevalol, epanolol, esmolol, indenolol, labetalol, levobunolol, mepindolol, metipranolol, metoprolol, moprolol, nadolol, nadoxolol, nebivalol, nifenalol, nipradilol, oxprenolol, penbutolol, pindolol, practolol, pronethalol, propranolol, sotalol, sulfinalol, talinolol, tertatolol, tilisolol, timolol, toliprolol, and xibenolol.

Examples of useful anticonvulsants include, but are not limited to, acetylpheneturide, albutoin, aloxidone, aminoglutethimide, 4-amino-3-hydroxybutyric acid, atrolactamide, beclamide, buramate, calcium bromide, carbamazepine, cinromide, clomethiazole, clonazepam, decimemide, diethadione, dimethadione, doxenitroin, eterobarb, ethadione, ethosuximide, ethotoin, felbamate, fluoresone, gabapentin, 5-hydroxytryptophan, lamotrigine, magnesium bromide, magnesium sulfate, mephenytoin, mephobarbital, metharbital, methetoin, methsuximide, 5-methyl-5-(3-phenanthryl)-hydantoin, 3-methyl-5-phenylhydantoin, narcobarbital, nimetazepam, nitrazepam, oxcarbazepine, paramethadione, phenacemide, phenetharbital, pheneturide, phenobarbital, phensuximide, phenylmethylbarbituric acid, phenytoin, phethenylate sodium, potassium bromide, pregabaline, primidone, progabide, sodium bromide, solanum, strontium bromide, suclofenide, sulthiame, tetrantoin, tiagabine, topiramate, trimethadione, valproic acid, valpromide, vigabatrin, and zonisamide.

Examples of useful antidepressants include, but are not limited to, binedaline, caroxazone, citalopram, dimethazan, fencamine, indalpine, indeloxazine hydrocholoride, nefopam, nomifensine, oxitriptan, oxypertine, paroxetine, sertraline, thiazesim, trazodone, benmoxine, iproclozide, iproniazid, isocarboxazid, nialamide, octamoxin, phenelzine, cotinine, rolicyprine, rolipram, maprotiline, metralindole, mianserin, mirtazepine, adinazolam, amitriptyline, amitriptylinoxide, amoxapine, butriptyline, clomipramine, demexiptiline, desipramine, dibenzepin, dimetacrine, dothiepin, doxepin, fluacizine, imipramine, imipramine N-oxide, iprindole, lofepramine, melitracen, metapramine, nortriptyline, noxiptilin, opipramol, pizotyline, propizepine, protriptyline, quinupramine, tianeptine, trimipramine, adrafinil, benactyzine, bupropion, butacetin, dioxadrol, duloxetine, etoperidone, febarbamate, femoxetine, fenpentadiol, fluoxetine, fluvoxamine, hematoporphyrin, hypericin, levophacetoperane, medifoxamine, milnacipran, minaprine, moclobemide, nefazodone, oxaflozane, piberaline, prolintane, pyrisuccideanol, ritanserin,

roxindole, rubidium chloride, sulpiride, tandospirone, thozalinone, tofenacin, toloxatone, tranylcypromine, L-tryptophan, venlafaxine, viloxazine, and zimeldine.

Examples of useful Ca2+-channel blockers include, but are not limited to, bepridil, clentiazem, diltiazem, fendiline, gallopamil, mibefradil, prenylamine, semotiadil, terodiline, verapamil, amlodipine, aranidipine, barnidipine, benidipine, cilnidipine, efonidipine, elgodipine, felodipine, isradipine, lacidipine, lercanidipine, manidipine, nicardipine, nifedipine, nilvadipine, nimodipine, nisoldipine, nitrendipine, cinnarizine, flunarizine, lidoflazine, lomerizine, bencyclane, etafenone, fantofarone, and perhexiline.

Examples of useful anticancer agents include, but are not limited to, acivicin, aclarubicin, acodazole hydrochloride, acronine, adozelesin, aldesleukin, altretamine, ambomycin, ametantrone acetate, aminoglutethimide, amsacrine, anastrozole, anthramycin, asparaginase, asperlin, azacitidine, azetepa, azotomycin, batimastat, benzodepa, bicalutamide, bisantrene hydrochloride, bisnafide dimesylate, bizelesin, bleomycin sulfate, brequinar sodium, bropirimine, busulfan, cactinomycin, calusterone, caracemide, carbetimer, carboplatin, carmustine, carubicin hydrochloride, carzelesin, cedefingol, chlorambucil, cirolemycin, cisplatin, cladribine, crisnatol mesylate, cyclophosphamide, cytarabine, dacarbazine, dactinomycin, daunorubicin hydrochloride, decitabine, dexormaplatin, dezaguanine, dezaguanine mesylate, diaziquone, docetaxel, doxorubicin, doxorubicin hydrochloride, droloxifene, droloxifene citrate, dromostanolone propionate, duazomycin, edatrexate, eflornithine hydrochloride, elsamitrucin, enloplatin, enpromate, epipropidine, epirubicin hydrochloride, erbulozole, esorubicin hydrochloride, estramustine, estramustine phosphate sodium, etanidazole, etoposide, etoposide phosphate, etoprine, fadrozole hydrochloride, fazarabine, fenretinide, floxuridine, fludarabine phosphate, fluorouracil, flurocitabine, fosquidone, fostriecin sodium, gemcitabine, gemcitabine hydrochloride, hydroxyurea, idarubicin hydrochloride, ifosfamide, ilmofosine, interleukin II (including recombinant interleukin II or rIL2), interferon alfa-2a, interferon alfa-2b, interferon alfa-n1 , interferon alfa-n3, interferon beta-I a, interferon gamma-I b, iproplatin, irinotecan hydrochloride, lanreotide acetate, letrozole, leuprolide acetate, liarozole hydrochloride, lometrexol sodium, lomustine, losoxantrone hydrochloride, masoprocol, maytansine, mechlorethamine hydrochloride, megestrol acetate, melengestrol acetate, melphalan, menogaril, mercaptopurine, methotrexate, methotrexate sodium, metoprine, meturedepa,

mitindomide, mitocarcin, mitocromin, mitogillin, mitomalcin, mitomycin, mitosper, mitotane, mitoxantrone hydrochloride, mycophenolic acid, nocodazole, nogalamycin, ormaplatin, oxisuran, paclitaxel, pegaspargase, peliomycin, pentamustine, peplomycin sulfate, perfosfamide, pipobroman, piposulfan, piroxantrone hydrochloride, plicamycin, plomestane, porfimer sodium, porfiromycin, prednimustine, procarbazine hydrochloride, puromycin, puromycin hydrochloride, pyrazofurin, riboprine, rogletimide, safingol, safingol hydrochloride, semustine, simtrazene, sparfosate sodium, sparsomycin, spirogermanium hydrochloride, spiromustine, spiroplatin, streptonigrin, streptozocin, sulofenur, talisomycin, tecogalan sodium, tegafur, teloxantrone hydrochloride, temoporfin, teniposide, teroxirone, testolactone, thiamiprine, thioguanine, thiotepa, tiazofurin, tirapazamine, toremifene citrate, trestolone acetate, triciribine phosphate, trimetrexate, trimetrexate glucuronate, triptorelin, tubulozole hydrochloride, uracil mustard, uredepa, vapreotide, verteporfin, vinblastine sulfate, vincristine sulfate, vindesine, vindesine sulfate, vinepidine sulfate, vinglycinate sulfate, vinleurosine sulfate, vinorelbine tartrate, vinrosidine sulfate, vinzolidine sulfate, vorozole, zeniplatin, zinostatin, zorubicin hydrochloride.

Examples of other anti-cancer drugs include, but are not limited to, 20-epi-1,25 dihydroxyvitamin D3; 5-ethynyluracil; abiraterone; aclarubicin; acylfulvene; adecypenol; adozelesin; aldesleukin; ALL-TK antagonists; altretamine; ambamustine; amidox; amifostine; aminolevulinic acid; amrubicin; amsacrine; anagrelide; anastrozole; andrographolide; angiogenesis inhibitors; antagonist D; antagonist G; antarelix; anti-dorsalizing morphogenetic protein-1; antiandrogen, prostatic carcinoma; antiestrogen; antineoplaston; antisense oligonucleotides; aphidicolin glycinate; apoptosis gene modulators; apoptosis regulators; apurinic acid; ara-CDP-DL-PTBA; arginine deaminase; asulacrine; atamestane; atrimustine; axinastatin 1; axinastatin 2; axinastatin 3; azasetron; azatoxin; azatyrosine; baccatin III derivatives; balanol; batimastat; BCR/ABL antagonists; benzochlorins; benzoylstaurosporine; beta lactam derivatives; beta-alethine; betaclamycin B; betulinic acid; bFGF inhibitor; bicalutamide; bisantrene; bisaziridinylspermine; bisnafide; bistratene A; bizelesin; breflate; bropirimine; budotitane; buthionine sulfoximine; calcipotriol; calphostin C; camptothecin derivatives; canarypox IL-2; capecitabine; carboxamide-amino-triazole; carboxyamidotriazole; CaRest M3; CARN 700; cartilage derived inhibitor; carzelesin; casein kinase inhibitors (ICOS); castanospermine; cecropin B;

cetrorelix; chlorlns; chloroquinoxaline sulfonamide; cicaprost; cis-porphyrin; cladribine; clomifene analogues; clotrimazole; collismycin A; collismycin B; combretastatin A4; combretastatin analogue; conagenin; crambescidin 816; crisnatol; cryptophycin 8; cryptophycin A derivatives; curacin A; cyclopentanthraquinones; cycloplatam; cypemycin; cytarabine ocfosfate; cytolytic factor; cytostatin; dacliximab; decitabine; dehydrodidemnin B; deslorelin; dexamethasone; dexifosfamide; dexrazoxane; dexverapamil; diaziquone; didemnin B; didox; diethylnorspermine; dihydro-5-azacytidine; dihydrotaxol, 9-; dioxamycin; diphenyl spiromustine; docetaxel; docosanol; dolasetron; doxifluridine; droloxifene; dronabinol; duocarmycin SA; ebselen; ecomustine; edelfosine; edrecolomab; eflornithine; elemene; emitefur; epirubicin; epristeride; estramustine analogue; estrogen agonists; estrogen antagonists; etanidazole; etoposide phosphate; exemestane; fadrozole; fazarabine; fenretinide; filgrastim; finasteride; flavopiridol; flezelastine; fluasterone; fludarabine; fluorodaunorunicin hydrochloride; forfenimex; formestane; fostriecin; fotemustine; gadolinium texaphyrin; gallium nitrate; galocitabine; ganirelix; gelatinase inhibitors; gemcitabine; glutathione inhibitors; hepsulfam; heregulin; hexamethylene bisacetamide; hypericin; ibandronic acid; idarubicin; idoxifene; idramantone; ilmofosine; ilomastat; imidazoacridones; imiquimod; immunostimulant peptides; insulin-like growth factor-1 receptor inhibitor; interferon agonists; interferons; interleukins; iobenguane; iododoxorubicin; ipomeanol, 4-; iroplact; irsogladine; isobengazole; isohomohalicondrin B; itasetron; jasplakinolide; kahalalide F; lamellarin-N triacetate; lanreotide; leinamycin; lenograstim; lentinan sulfate; leptolstatin; letrozole; leukemia inhibiting factor; leukocyte alpha interferon; leuprolide+estrogen+progesterone; leuprorelin; levamisole; liarozole; linear polyamine analogue; lipophilic disaccharide peptide; lipophilic platinum compounds; lissoclinamide 7; lobaplatin; lombricine; lometrexol; lonidamine; losoxantrone; lovastatin; loxoribine; lurtotecan; lutetium texaphyrin; lysofylline; lytic peptides; maitansine; mannostatin A; marimastat; masoprocol; maspin; matrilysin inhibitors; matrix metalloproteinase inhibitors; menogaril; merbarone; meterelin; methioninase; metoclopramide; MIF inhibitor; mifepristone; miltefosine; mirimostim; mismatched double stranded RNA; mitoguazone; mitolactol; mitomycin analogues; mitonafide; mitotoxin fibroblast growth factor-saporin; mitoxantrone; mofarotene; molgramostim; monoclonal antibody, human chorionic gonadotrophin; monophosphoryl lipid A+myobacterium cell wall sk; mopidamol; multiple

drug resistance gene inhibitor; multiple tumor suppressor 1-based therapy; mustard anticancer agent; mycaperoxide B; mycobacterial cell wall extract; myriaporone; N-acetyldinaline; N-substituted benzamides; nafarelin; nagrestip; naloxone+pentazocine; napavin; naphterpin; nartograstim; nedaplatin; nemorubicin; neridronic acid; neutral endopeptidase; nilutamide; nisamycin; nitric oxide modulators; nitroxide antioxidant; nitrullyn; O6-benzylguanine; octreotide; okicenone; oligonucleotides; onapristone; ondansetron; ondansetron; oracin; oral cytokine inducer; ormaplatin; osaterone; oxaliplatin; oxaunomycin; paclitaxel; paclitaxel analogues; paclitaxel derivatives; palauamine; palmitoylrhizoxin; pamidronic acid; panaxytriol; panomifene; parabactin; pazelliptine; pegaspargase; peldesine; pentosan polysulfate sodium; pentostatin; pentrozole; perflubron; perfosfamide; perillyl alcohol; phenazinomycin; phenylacetate; phosphatase inhibitors; picibanil; pilocarpine hydrochloride; pirarubicin; piritrexim; placetin A; placetin B; plasminogen activator inhibitor; platinum complex; platinum compounds; platinum-triamine complex; porfimer sodium; porfiromycin; prednisone; propyl bis-acridone; prostaglandin J2; proteasome inhibitors; protein A-based immune modulator; protein kinase C inhibitor; protein kinase C inhibitors, microalgal; protein tyrosine phosphatase inhibitors; purine nucleoside phosphorylase inhibitors; purpurins; pyrazoloacridine; pyridoxylated hemoglobin polyoxyethylene conjugate; raf antagonists; raltitrexed; ramosetron; ras farnesyl protein transferase inhibitors; ras inhibitors; ras-GAP inhibitor; retelliptine demethylated; rhenium Re 186 etidronate; rhizoxin; ribozymes; RII retinamide; rogletimide; rohitukine; romurtide; roquinimex; rubiginone B1; ruboxyl; safingol; saintopin; SarCNU; sarcophytol A; sargramostim; Sdi 1 mimetics; semustine; senescence derived inhibitor 1; sense oligonucleotides; signal transduction inhibitors; signal transduction modulators; single chain antigen binding protein; sizofiran; sobuzoxane; sodium borocaptate; sodium phenylacetate; solverol; somatomedin binding protein; sonermin; sparfosic acid; spicamycin D; spiromustine; splenopentin; spongistatin 1; squalamine; stem cell inhibitor; stem-cell division inhibitors; stipiamide; stromelysin inhibitors; sulfinosine; superactive vasoactive intestinal peptide antagonist; suradista; suramin; swainsonine; synthetic glycosaminoglycans; tallimustine; tamoxifen methiodide; tauromustine; tazarotene; tecogalan sodium; tegafur; tellurapyrylium; telomerase inhibitors; temoporfin; temozolomide; teniposide; tetrachlorodecaoxide; tetrazomine; thaliblastine; thiocoraline; thrombopoietin; thrombopoietin mimetic; thymalfasin; thymopoietin receptor

agonist; thymotrinan; thyroid stimulating hormone; tin ethyl etiopurpurin; tirapazamine; titanocene bichloride; topsentin; toremifene; totipotent stem cell factor; translation inhibitors; tretinoin; triacetyluridine; triciribine; trimetrexate; triptorelin; tropisetron; turosteride; tyrosine kinase inhibitors; tyrphostins; UBC inhibitors; ubenimex; urogenital sinus-derived growth inhibitory factor; urokinase receptor antagonists; vapreotide; variolin B; vector system, erythrocyte gene therapy; velaresol; veramine; verdins; verteporfin; vinorelbine; vinxaltine; vitaxin; vorozole; zanoterone; zeniplatin; zilascorb; and zinostatin stimalamer.

Examples of useful therapeutic agents for treating or preventing UI include, but are not limited to, propantheline, imipramine, hyoscyamine, oxybutynin, and dicyclomine.

Examples of useful therapeutic agents for treating or preventing an ulcer include, antacids such as aluminum hydroxide, magnesium hydroxide, sodium bicarbonate, and calcium bicarbonate; sucraflate; bismuth compounds such as bismuth subsalicylate and bismuth subcitrate; H_2 antagonists such as cimetidine, ranitidine, famotidine, and nizatidine; H^+, K^+ - ATPase inhibitors such as omeprazole, iansoprazole, and lansoprazole; carbenoxolone; misprostol; and antibiotics such as tetracycline, metronidazole, timidazole, clarithromycin, and amoxicillin.

Examples of useful therapeutic agents for treating or preventing IBD include, but are not limited to, anticholinergic drugs; diphenoxylate; loperamide; deodorized opium tincture; codeine; broad-spectrum antibiotics such as metronidazole; sulfasalazine; olsalazie; mesalamine; prednisone; azathioprine; mercaptopurine; and methotrexate.

Examples of useful therapeutic agents for treating or preventing IBS include, but are not limited to, propantheline; muscarine receptor antogonists such as pirenzapine, methoctramine, ipratropium, tiotropium, scopolamine, methscopolamine, homatropine, homatropine methylbromide, and methantheline; and antidiarrheal drugs such as diphenoxylate and loperamide.

Examples of useful therapeutic agents for treating or preventing an addictive disorder include, but are not limited to, methadone, desipramine, amantadine, fluoxetine, buprenorphine, an opiate agonist, 3-phenoxypyridine, levomethadyl acetate hydrochloride, and serotonin antagonists.

Examples of useful therapeutic agents for treating or preventing Parkinson's disease and parkinsonism include, but are not limited to, carbidopa/levodopa, pergolide,

bromocriptine, ropinirole, pramipexole, entacapone, tolcapone, selegiline, amantadine, and trihexyphenidyl hydrochloride.

Examples of useful therapeutic agents for treating or preventing anxiety include, but are not limited to, benzodiazepines, such as alprazolam, brotizolam, chlordiazepoxide, clobazam, clonazepam, clorazepate, demoxepam, diazepam, estazolam, flumazenil, flurazepam, halazepam, lorazepam, midazolam, nitrazepam, nordazepam, oxazepam, prazepam, quazepam, temazepam, and triazolam; non-benzodiazepine agents, such as buspirone, gepirone, ipsaprione, tiospirone, zolpicone, zolpidem, and zaleplon; tranquilizers, such as barbituates, *e.g.*, amobarbital, aprobarbital, butabarbital, butalbital, mephobarbital, methohexital, pentobarbital, phenobarbital, secobarbital, and thiopental; and propanediol carbamates, such as meprobamate and tybamate.

Examples of useful therapeutic agents for treating or preventing epilepsy include, but are not limited to, carbamazepine, ethosuximide, gabapentin, lamotrignine, phenobarbital, phenytoin, primidone, valproic acid, trimethadione, bemzodiaepines, gabapentin, lamotrigine, γ-vinyl GABA, acetazolamide, and felbamate.

Examples of useful therapeutic agents for treating or preventing stroke include, but are not limited to, anticoagulants such as heparin, agents that break up clots such as streptokinase or tissue plasminogen activator, agents that reduce swelling such as mannitol or corticosteroids, and acetylsalicylic acid.

Examples of useful therapeutic agents for treating or preventing a seizure include, but are not limited to, carbamazepine, ethosuximide, gabapentin, lamotrignine, phenobarbital, phenytoin, primidone, valproic acid, trimethadione, bemzodiaepines, gabapentin, lamotrigine, γ-vinyl GABA, acetazolamide, and felbamate.

Examples of useful therapeutic agents for treating or preventing a pruritic condition include, but are not limited to, naltrexone; nalmefene; danazol; tricyclics such as amitriptyline, imipramine, and doxepin; antidepressants such as those given below, menthol; camphor; phenol; pramoxine; capsaicin; tar; steroids; and antihistamines.

Examples of useful therapeutic agents for treating or preventing psychosis include, but are not limited to, phenothiazines such as chlorpromazine hydrochloride, mesoridazine besylate, and thoridazine hydrochloride; thioxanthenes such as chloroprothixene and thiothixene hydrochloride; clozapine; risperidone; olanzapine;

quetiapine; quetiapine fumarate; haloperidol; haloperidol decanoate; loxapine succinate; molindone hydrochloride; pimozide; and ziprasidone.

Examples of useful therapeutic agents for treating or preventing Huntington's chorea include, but are not limited to, haloperidol and pimozide.

Examples of useful therapeutic agents for treating or preventing ALS include, but are not limited to, baclofen, neurotrophic factors, riluzole, tizanidine, benzodiazepines such as clonazepan and dantrolene.

Examples of useful therapeutic agents for treating or preventing cognitive disorders include, but are not limited to, agents for treating or preventing dementia such as tacrine; donepezil; ibuprofen; antipsychotic drugs such as thioridazine and haloperidol; and antidepressant drugs such as those given below.

Examples of useful therapeutic agents for treating or preventing a migraine include, but are not limited to, sumatriptan; methysergide; ergotamine; caffeine; and beta-blockers such as propranolol, verapamil, and divalproex.

Examples of useful therapeutic agents for treating or preventing vomiting include, but are not limited to, 5-HT_3 receptor antagonists such as ondansetron, dolasetron, granisetron, and tropisetron; dopamine receptor antagonists such as prochlorperazine, thiethylperazine, chlorpromazin, metoclopramide, and domperidone; glucocorticoids such as dexamethasone; and benzodiazepines such as lorazepam and alprazolam.

Examples of useful therapeutic agents for treating or preventing dyskinesia include, but are not limited to, reserpine and tetrabenazine.

Examples of useful therapeutic agents for treating or preventing depression include, but are not limited to, tricyclic antidepressants such as amitryptyline, amoxapine, bupropion, clomipramine, desipramine, doxepin, imipramine, maprotilinr, nefazadone, nortriptyline, protriptyline, trazodone, trimipramine, and venlaflaxine; selective serotonin reuptake inhibitors such as fluoxetine, fluvoxamine, paroxetine, and setraline; monoamine oxidase inhibitors such as isocarboxazid, pargyline, phenelzine, and tranylcypromine; and psychostimulants such as dextroamphetamine and methylphenidate.

A Cyanoiminopiperazine Compound and the other therapeutic agent can act additively or, in one embodiment, synergistically. In one embodiment, a Cyanoiminopiperazine Compound is administered concurrently with another therapeutic

agent. In one embodiment, a composition comprising an effective amount of a Cyanoiminopiperazine Compound and an effective amount of another therapeutic agent can be administered. Alternatively, a composition comprising an effective amount of a Cyanoiminopiperazine Compound and a different composition comprising an effective amount of another therapeutic agent can be concurrently administered. In another embodiment, an effective amount of a Cyanoiminopiperazine Compound is administered prior or subsequent to administration of an effective amount of another therapeutic agent. In this embodiment, the Cyanoiminopiperazine Compound is administered while the other therapeutic agent exerts its therapeutic effect, or the other therapeutic agent is administered while the Cyanoiminopiperazine Compound exerts its preventative or therapeutic effect for treating or preventing a Condition.

A composition of the invention is prepared by a method comprising admixing a Cyanoiminopiperazine Compound or a pharmaceutically acceptable salt and a pharmaceutically acceptable carrier or excipient. Admixing can be accomplished using methods well known for admixing a compound (or salt) and a pharmaceutically acceptable carrier or excipient. In one embodiment the Cyanoiminopiperazine Compound or the pharmaceutically acceptable salt of the Compound is present in the composition in an effective amount.

4.19.2 Kits

The invention encompasses kits that can simplify the administration of a Cyanoiminopiperazine Compound to an animal.

A typical kit of the invention comprises a unit dosage form of a Cyanoiminopiperazine Compound. In one embodiment, the unit dosage form is a container, which can be sterile, containing an effective amount of a Cyanoiminopiperazine Compound and a pharmaceutically acceptable carrier or excipient. The kit can further comprise a label or printed instructions instructing the use of the Cyanoiminopiperazine Compound to treat pain, UI, an ulcer, IBD, IBS, an addictive disorder, Parkinson's disease, parkinsonism, anxiety, epilepsy, stroke, a seizure, a pruritic condition, psychosis, a cognitive disorder, a memory deficit, restricted brain function, Huntington's chorea, ALS, dementia, retinopathy, a muscle spasm, a migraine, vomiting, dyskinesia, or depression. The kit can also further comprise a

unit dosage form of another therapeutic agent, for example, a container containing an effective amount of the other therapeutic agent. In one embodiment, the kit comprises a container containing an effective amount of a Cyanoiminopiperazine Compound and an effective amount of another therapeutic agent. Examples of other therapeutic agents include, but are not limited to, those listed above.

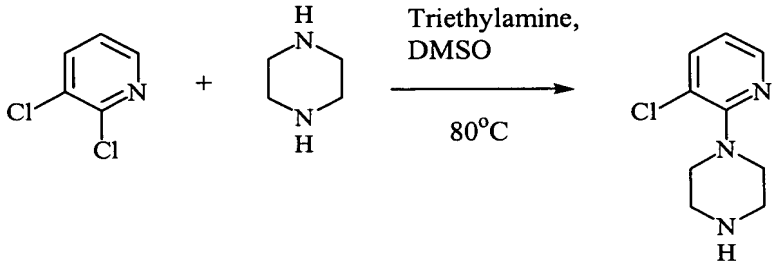
Kits of the invention can further comprise a device that is useful for administering the unit dosage forms. Examples of such a device includes, but are not limited to, a syringe, a drip bag, a patch, an inhaler, and an enema bag.

The following examples are set forth to assist in understanding the invention and should not, of course, be construed as specifically limiting the invention described and claimed herein. Such variations of the invention, including the substitution of all equivalents now known or later developed, which would be within the purview of those skilled in the art, and changes in formulation or minor changes in experimental design, are to be considered to fall within the scope of the invention incorporated herein.

5. EXAMPLES

Examples 1-3 relate to the synthesis of illustrative Cyanoiminopiperazine Compounds.

5.1. Example 1: Synthesis of Compound AAA



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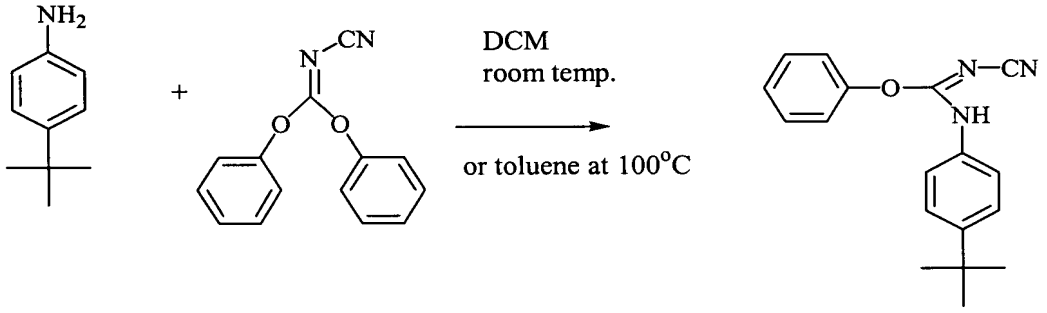

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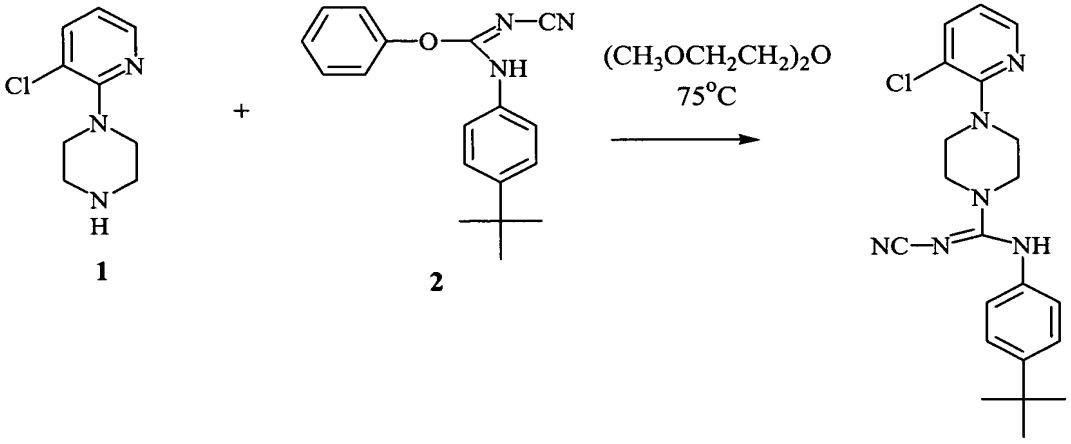


1 2

Compound AAA

2,3-Dichloropyridine (15.0 g, 101.6 mmol), piperazine(9.78 g, 113.70 mmol), and triethylamine (14.36 g, 141.95 mmol) were dissolved in 300 mL of DMSO and the resulting mixture was heated at about 80°C for about 24 h. The reaction mixture was then cooled to room temperature and extracted with a saturated aqueous sodium bicarbonate solution. The organic layer was dried, concentrated, and purified using a silica gel column eluted with a gradient elution from ethyl acetate to 2:1 ethyl acetate:methanol to provide N-(3-chloropyridin-2-yl)-piperazine (compound **1**) as a yellow liquid.

A solution diphenylcyanocarbodimidate (Commercially available from Sigma-Aldrich, St. Louis, MO (www.sigma-aldrich.com)) (0.5 mmol) and 4-*tert*-butylaniline (0.5 mmol) in 1.5 mL of DCM was stirred at room temperature for about 12 h. The mixture was concentrated under reduced pressure to provide compound **2**, which was used directly in the next step without further purification.

A solution of compound **2**, prepared as described above, and compound **1** (0.5 mmol), prepared as described above, in 1.5 mL of 2-methoxymethylether was stirred at about 75°C for about 12 h. The solution was cooled to room temperature and purified using direct flash chromatography on a silica gel column eluted with a gradient elution from 1:10 ethyl acetate:hexane to 1:1 ethyl acetate:hexane to provide Compound **AAA** (62 % yield).

The identity of compound **AAA** was confirmed using ^{1}H NMR.

Compound **AAA**: ^{1}H NMR ($CDCl_3$) δ 9.19(dd, J = 1.5, 4.7 Hz, 1H), 6.62 (dd, J = 1.5, 7.8 Hz, 1H), 7.38 (d, J = 8.5 Hz, 2H), 7.18 (b, 1H), 7.01 (d, J = 8.5 Hz, 2H), 6.91 (dd, J = 4.7, 7.8 Hz, 1H), 3.58 (m, 4H), 3.34 (m, 4H), 1.33 (s, 9H) ppm.

5.2. Example 2: Synthesis of Compound AAI

Compound **AAI** was prepared by a procedure analogous to that used to prepare Compound **AAA** except that 4-trifluoromethoxyaniline was used in place of 4-*tert*-butylaniline (yield 78%).

The identity of compound **AAI** was confirmed using ^{1}H NMR.

Compound **AAI**: ^{1}H NMR ($CDCl_3$) δ 8.19(dd, J = 1.6, 4.7 Hz, 1H), 7.62 (dd, J = 1.6, 7.8 Hz, 1H), 7.26 (b, 1H), 7.24 (d, J = 9.0 Hz, 2H), 7.12 (d, J = 9.0 Hz, 2H), 6.92 (dd, J = 4.7 Hz, 1H), 3.59 (m, 4H), 3.35 (m, 4H) ppm.

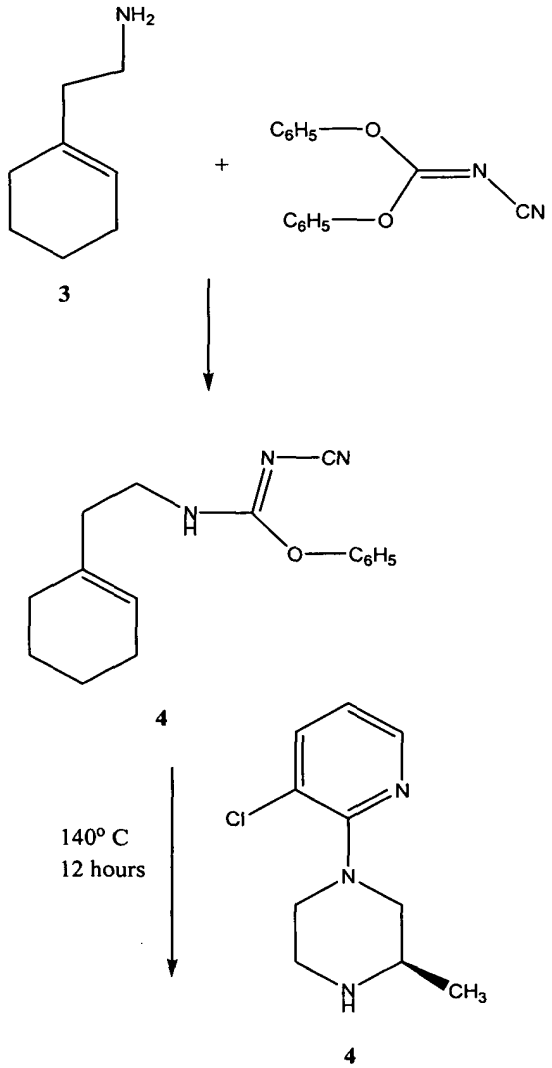
5.3. Example 3: Synthesis of Compound AAG

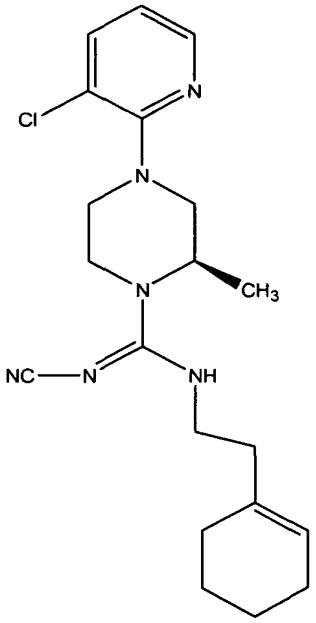
Compound **AAG** was prepared by a procedure analogous to that used to prepare Compound **AAA** except that 4-trifluoromethylaniline was used in place of 4-*tert*-butylaniline (yield 61%).

The identity of compound **AAG** was confirmed using ^{1}H NMR.

Compound **AAG**: ^{1}H NMR ($CDCl_3$) δ 8.19(dd, J = 1.6, 4.7 Hz, 1H), 7.62 (dd, J = 1.6, 7.8 Hz, 1H), 7.26 (b, 1H), 7.24 (d, J = 9.0 Hz, 2H), 7.12 (d, J = 9.0 Hz, 2H), 6.92 (dd, J = 4.7 Hz, 1H), 3.59 (m, 4H), 3.35 (m, 4H) ppm.

5.4. Example 4: Synthesis of Compound DEY





Compound DEY

To a solution of 2-(1-cyclohexenyl)-ethylamine **3** (125.2 mg, 1.0 mmol) in 2-methoxyethyl ether (2.0 mL) was added diphenylcyanocarbodimidate (commercially available from Sigma-Aldrich, St. Louis, MO (www.sigma-aldrich.com)) (238.2 mg, 1.0 mmol) at room temperature. The resultant reaction mixture was heated to about 80° C and allowed to stir at 80° C for about 5 h. (R)-1-(3-chloro-pyridin-2-yl)-3-methylpiperazine **4** (211.6 mg, 1.0 mmol) was added to the reaction mixture and the reaction mixture was heated to about 140° C and allowed to stir at about 140° C for about 12 h. The reaction mixture was then cooled to room temperature and purified using flash chromatography on a silica gel column eluted with ethyl acetate/hexane (10:90 to 50:50) to provide compound **DEY** as a slightly yellow product.

Compound **4** was prepared by a procedure analogous to that used to prepare Compound **1**, as described above in Example 1, except that (R)-3-methylpiperazine (commercially available from Sigma-Aldrich, St. Louis, MO (www.sigma-aldrich.com)) was used in place of piperazine.

The identity of compound **DEY** was confirmed using ^{1}H NMR and mass spectroscopy (MS).

Compound **DEY**: ^{1}H NMR ($CDCl_3$) δ 8.20 (dd, J = 1.8, 4.9 Hz, 1H), 7.63 (dd, J = 1.8, 7.8 Hz, 1H), 6.91 (dd, J= 4.9, 7.8 Hz, 1H), 5.61 (br, s, 1H), 4.80 (m, 1H), 4,32 (m, 1H), 3.80 (m, 3H), 3.63 (m, 2H), 3.42 (m, 1H), 3.10 (m, 1H), 3.00 (m, 1H), 2.31 (m, 1H), 2.05 (m, 2H), 1.96 (m, 2H), 1.64 (m, 5H), 1.43 (m, 3H) ppm.

MS: m/e 387.6

5.5. Example 5: Binding of Cyanoiminopiperazine Compounds to mGluR5

The following assay can be used to demonstrates Cyanoiminopipereazine Compounds that bind to and modulate the activity of mGluR5.

Cell cultures: Primary glial cultures are prepared from cortices of Sprague-Dawley 18 days old embryos. The cortices are dissected and then dissociated by trituration. The resulting cell homogenate is plated onto poly-D-lysine precoated T175 flasks (BIOCOAT, commercially available from Becton Dickinson and Company Inc. of Franklin Lakes, NJ) in Dulbelcco's Modified Eagle's Medium ("DMEM," pH 7.4), buffered with 25 mM HEPES, and supplemented with 15% fetal calf serum ("FCS," commercially available from Hyclone Laboratories Inc. of Omaha, NE), and incubated at 37°C and 5% CO_2. After 24 hours, FCS supplementation is reduced to 10%. On day six, oligodendrocytes and microglia are removed by strongly tapping the sides of the flasks. One day following this purification step, secondary astrocyte cultures are established by subplating onto 96 poly-D-lysine precoated T175 flasks (BIOCOAT) at a density of 65,000 cells/well in DMEM and 10% FCS. After 24 hours, the astrocytes are washed with serum free medium and then cultured in DMEM, without glutamate, supplemented with 0.5% FCS, 20 mM HEPES, 10 ng/mL epidermal growth factor ("EGF"), 1 mM sodium pyruvate, and 1X penicillin/streptomycin at pH 7.5 for 3 to 5 days at 37°C and 5% CO_2. The procedure allows the expression of the mGluR5 receptor by astrocytes, as demonstrated by S. Miller *et al.*, *J. Neuroscience* 15(9):6103-6109 (1995).

Assay Protocol: After 3-5 days incubation with EGF, the astrocytes are washed with 127 mM NaCl, 5 mM KCl, 2 mM $MgCl_2$, 700 mM NaH_2PO_4, 2 mM $CaCl_2$, 5 mM $NaHCO_3$, 8 mM HEPES, 10 mM Glucose at pH 7.4 ("Assay Buffer") and loaded with the dye Fluo-4 (commercially available from Molecular Probes Inc. of Eugene, OR) using 0.1 mL of Assay Buffer containing Fluo-4 (3 mM final). After 90 minutes of dye loading, the cells are then washed twice with 0.2 mL Assay Buffer and resuspended in 0.1 mL of Assay Buffer. The

plates containing the astrocytes are then transferred to a Fluorometric Imaging Plate reader (commercially available from Molecular Devices Corporation of Sunnyvale, CA) for the assessment of calcium mobilization flux in the presence of glutamate and in the presence or absence of antagonist. After monitoring fluorescence for 15 seconds to establish a base line, DMSO solutions containing various concentrations of a Cyanoiminopipereazine Compound diluted in Assay Buffer (0.05 mL of 4X dilutions for competition curves) are added to the cell plate and fluorescence is monitored for 2 minutes. 0.05 mL of a 4X glutamate solution (agonist) is then added to each well to provide a final glutamate concentration in each well of 10 mM. Plate fluorescence is then monitored for an additional 60 seconds after agonist addition. The final DMSO concentration in the assay is 1.0%. In each experiment, fluorescence is monitored as a function of time and the data analyzed using Microsoft Excel and GraphPad Prism. Dose-response curves are fit using a non-linear regression to determine IC_{50} value. In each experiment, each data point is determined two times. The assay results will demonstrate that Cyanoiminopipereazine Compounds bind to and modulate the activity of mGluR5.

5.6 EXAMPLE 6: BINDING OF CYANOIMINOPIPERAZINE COMPOUNDS TO MGLUR5

Alternatively, the following assay can be used to demonstrate that a Cyanoiminopiperazine Compound binds to and modulates the activity of mGluR5.

40,000 CHO-rat mGluR5 cells/well are plated into 96 well plate (Costar 3409, Black, clear bottom, 96 well, tissue culture treated) for an overnight incubation in Dulbecco's Modified Eagle's Medium (DMEM, pH 7.4) and supplemented with glutamine, 10% FBS, 1% Pen/Strep, and 500ug/mL Geneticin. CHO-rat mGluR5 cells are washed and treated with Optimem medium and were incubated for 1-4 hours prior to loading cells. Cell plates are washed with loading buffer (127 mM NaCl, 5 mM KCl, 2 mM $MgCl_2$, 700 μM Na H_2PO_4, 2 mM $CaCl_2$, 5 mM $NaHCO_3$, 8 mM Hepes, and 10 mM glucose, pH 7.4) and incubated with 3μM Fluo 4 (commercially available from Molecular probes Inc. of Eugene, OR) in 0.1 mL of loading buffer. After 90 minutes of dye loading, the cells are washed twice with 0.2 mL loading buffer and resuspended in 0.1 mL loading buffer.

The plates containing the CHO-rat mGluR5 cells are transferred to a Fluorometric Imaging Plate Reader (FLIPR) (commercially available from Molecular Devices Corporation of Sunnyvale, CA) for the assessment of calcium mobilization flux in the presence of glutamate and in the presence or absence of test compounds. After monitoring fluorescence for 15 seconds to establish a baseline, DMSO solutions containing various concentrations of the test compound diluted in loading buffer (0.05 mL of 4X dilutions for the competition curves) are added to the cell plate and fluorescence was monitored for 2 minutes. 0.05 mL of 4X glutamate solution (agonist) is then added to each well to provide a final glutamate concentration in each well of 10 uM. Plate fluorescence is then monitored for an additional 60 seconds after agonist addition. The final DMSO concentration in the assay is 1.0%. In each experiment, fluorescence is monitored as a function of time and the data analyzed using Microsoft Excel and GraphPad Prism. Dose-response curves are fit using a non-linear regression to determine the IC50 value. In each experiment, each data point is determined at least two times.

5.7. Example 7: *In Vivo* Assays for Prevention or Treatment of Pain

Test Animals: Each experiment uses rats weighing between 200-260 g at the start of the experiment. The rats are group-housed and have free access to food and water at all times, except prior to oral administration of a Cyanoiminopiperazine Compound when food is removed for 16 hours before dosing. A control group acts as a comparison to rats treated with a Cyanoiminopiperazine Compound. The control group is administered the carrier for the Cyanoiminopiperazine Compound. The volume of carrier administered to the control group is the same as the volume of carrier and Cyanoiminopiperazine Compound administered to the test group.

Acute Pain: To assess the actions of the Cyanoiminopiperazine Compounds for the treatment or prevention of acute pain the rat tail flick test can be used. Rats are gently restrained by hand and the tail exposed to a focused beam of radiant heat at a point 5 cm from the tip using a tail flick unit (Model 7360, commercially available from Ugo Basile of Italy). Tail flick latencies are defined as the interval between the onset of the thermal stimulus and the flick of the tail. Animals not responding within 20 seconds are removed from the tail flick unit and assigned a withdrawal latency of 20 seconds. Tail flick latencies are measured

immediately before (pre-treatment) and 1, 3, and 5 hours following administration of a Cyanoiminopiperazine Compound. Data are expressed as tail flick latency(s) and the percentage of the maximal possible effect (% MPE), *i.e.*, 20 seconds, is calculated as follows:

$$\% \text{ MPE} = \frac{[\text{(post administration latency)} - \text{(pre-administration latency)}]}{\text{(20 s pre-administration latency)}} \times 100$$

The rat tail flick test is described in F.E. D'Amour *et al.*, "A Method for Determining Loss of Pain Sensation," *J. Pharmacol. Exp. Ther.* 72:74-79 (1941). The results show that Cyanoiminopiperazine Compounds are useful for treating or preventing acute pain.

Acute pain can also be assessed by measuring the animal's response to noxious mechanical stimuli by determining the paw withdrawal threshold ("PWT"), as described below.

Inflammatory Pain: To assess the actions of the Cyanoiminopiperazine Compounds for the treatment or prevention of inflammatory pain the Freund's complete adjuvant ("FCA") model of inflammatory pain is used. FCA-induced inflammation of the rat hind paw is associated with the development of persistent inflammatory mechanical hyperalgesia and provides reliable prediction of the anti-hyperalgesic action of clinically useful analgesic drugs (L. Bartho *et al.*, "Involvement of Capsaicin-sensitive Neurones in Hyperalgesia and Enhanced Opioid Antinociception in Inflammation," *Naunyn-Schmiedeberg's Archives of Pharmacology* 342:666-670 (1990)). The left hind paw of each animal is administered a 50 µL intraplantar injection of 50% FCA. 24 hour post injection, the animal is assessed for response to noxious mechanical stimuli by determining the PWT, as described below. Rats are then administered a single injection of 1, 3, 10 or 30 mg/Kg of either a Cyanoiminopiperazine Compound, 30 mg/Kg of a control selected from indomethacin, Celebrex or naproxen or carrier. Responses to noxious mechanical stimuli are then determined 1, 3, 5, and 24 hours post administration. Percentage reversal of hyperalgesia for each animal is defined as:

$$\% \text{ Reversal} = \frac{[\text{(post administration PWT)} - \text{(pre-administration PWT)}]}{[\text{(Baseline PWT)} - \text{(pre-administration PWT)}]} \times 100$$

The results show that the Cyanoiminopiperazine Compounds are useful for treating or preventing inflammatory pain.

Neuropathic Pain: To assess the actions of the Cyanoiminopiperazine Compounds for the treatment or prevention of neuropathic pain either the Seltzer model or the Chung model can be used.

In the Seltzer model, the partial sciatic nerve ligation model of neuropathic pain is used to produce neuropathic hyperalgesia in rats (Z. Seltzer *et al.*, "A Novel Behavioral Model of Neuropathic Pain Disorders Produced in Rats by Partial Sciatic Nerve Injury," *Pain* 43:205-218 (1990)). Partial ligation of the left sciatic nerve is performed under isoflurane/O_2 inhalation anaesthesia. Following induction of anesthesia, the left thigh of the rat is shaved and the sciatic nerve exposed at high thigh level through a small incision and is carefully cleared of surrounding connective tissues at a site near the trocanther just distal to the point at which the posterior biceps semitendinosus nerve branches off of the common sciatic nerve. A 7-0 silk suture is inserted into the nerve with a 3/8 curved, reversed-cutting mini-needle and tightly ligated so that the dorsal 1/3 to ½ of the nerve thickness is held within the ligature. The wound is closed with a single muscle suture (4-0 nylon (Vicryl)) and a Vetbond surgical glue. Following surgery, the wound area is dusted with antibiotic powder. Sham-treated rats undergo an identical surgical procedure except that the sciatic nerve is not manipulated. Following surgery, animals are weighed and placed on a warm pad until they recover from anesthesia. Animals are then returned to their home cages until behavioral testing begins. The animal is assessed for response to noxious mechanical stimuli by determining PWT, as described below, prior to surgery (baseline), then immediately prior to and 1, 3, and 5 hours after drug administration for the left rear paw of the animal. Percentage reversal of neuropathic hyperalgesia is defined as:

$$\% \text{ Reversal} = \frac{[(\text{post administration PWT}) - (\text{pre-administration PWT})]}{[(\text{Baseline PWT}) - (\text{pre-administration PWT})]} \times 100$$

In the Chung model, the spinal nerve ligation model of neuropathic pain is used to produce mechanical hyperalgesia, thermal hyperalgesia and tactile allodynia in rats. Surgery is performed under isoflurane/O_2 inhalation anaesthesia. Following induction of anaesthesia a 3 cm incision is made and the left paraspinal muscles are separated from the spinous process at the L_4 - S_2 levels. The L_6 transverse process is carefully removed with a pair of small rongeurs to identify visually the L_4 - L_6 spinal nerves. The left L_5 (or L_5 and L_6) spinal nerve(s) is isolated and tightly ligated with silk thread. A complete hemostasis is confirmed and the wound is sutured using non-absorbable sutures, such as nylon sutures or stainless steel staples. Sham-treated rats undergo an identical surgical procedure except that the spinal nerve(s) is not manipulated. Following surgery animals are weighed, administered a subcutaneous (s.c.) injection of saline or ringers lactate, the wound area is dusted with antibiotic powder and they are kept on a warm pad until they recover from the anesthesia. Animals are then returned to their home cages until behavioral testing begins. The animals are assessed for response to noxious mechanical stimuli by determining PWT, as described below, prior to surgery (baseline), then immediately prior to and 1, 3, and 5 hours after being administered a Cyanoiminopiperazine Compound for the left rear paw of the animal. The animal can also be assessed for response to noxious thermal stimuli or for tactile allodynia, as described below. The Chung model for neuropathic pain is described in S.H. Kim, "An Experimental Model for Peripheral Neuropathy Produced by Segmental Spinal Nerve Ligation in the Rat," *Pain* 50(3):355-363 (1992). The results will show that Cyanoiminopiperazine Compounds are useful for treating or preventing neuropathic pain.

Response to Mechanical Stimuli as an Assessment of Mechanical Hyperalgesia: The paw pressure assay can be used to assess mechanical hyperalgesia. For this assay, hind paw withdrawal thresholds (PWT) to a noxious mechanical stimulus are determined using an analgesymeter (Model 7200, commercially available from Ugo Basile of Italy) as described in C. Stein, "Unilateral Inflammation of the Hindpaw in Rats as a Model of Prolonged Noxious Stimulation: Alterations in Behavior and Nociceptive Thresholds," *Pharmacology*

Biochemistry and Behavior 31:451-455 (1988). The maximum weight that can be applied to the hind paw is set at 250 g and the end point is taken as complete withdrawal of the paw. PWT is determined once for each rat at each time point and only the affected (ipsilateral) paw is tested.

Response to Thermal Stimuli as an Assessment of Thermal Hyperalgesia: The plantar test can be used to assess thermal hyperalgesia. For this test, hind paw withdrawal latencies to a noxious thermal stimulus are determined using a plantar test apparatus (commercially available from Ugo Basile of Italy) following the technique described by K. Hargreaves *et al.*, "A New and Sensitive Method for Measuring Thermal Nociception in Cutaneous Hyperalgesia," *Pain* 32(1):77-88 (1988). The maximum exposure time is set at 32 seconds to avoid tissue damage and any directed paw withdrawal from the heat source is taken as the end point. Three latencies are determined at each time point and averaged. Only the affected (ipsilateral) paw is tested.

Assessment of Tactile Allodynia: To assess tactile allodynia, rats are placed in clear, plexiglass compartments with a wire mesh floor and allowed to habituate for a period of at least 15 minutes. After habituation, a series of von Frey monofilaments are presented to the plantar surface of the left (operated) foot of each rat. The series of von Frey monofilaments consists of six monofilaments of increasing diameter, with the smallest diameter fiber presented first. Five trials are conducted with each filament with each trial separated by approximately 2 minutes. Each presentation lasts for a period of 4-8 seconds or until a nociceptive withdrawal behavior is observed. Flinching, paw withdrawal or licking of the paw are considered nociceptive behavioral responses.

5.8. Example 8: *In Vivo* Assays for Prevention or Treatment of Anxiety

The elevated plus maze test or the shock-probe burying test can be used to assess the anxiolytic activity of Cyanoiminopipereazine Compounds in rats or mice.

The Elevated Plus Maze Test: The elevated plus maze consists of a platform with 4 arms, two open and two closed (50x10x50 cm enclosed with an open roof). Rats (or mice) are placed in the center of the platform, at the crossroad of the 4 arms, facing one of the closed arms. Time spent in the open arms vs the closed arms and number of open arm entries

during the testing period are recorded. This test is conducted prior to drug administration and again after drug administration. Test results are expressed as the mean time spent in open arms and the mean number of entries into open arms. Known anxiolytic drugs increase both the time spent in open arms and number of open arm entries. The elevated plus maze test is described in D. Treit, "Animal Models for the Study of Anti-anxiety Agents: A Review," *Neuroscience & Biobehavioral Reviews* 9(2):203-222 (1985).

The Shock-Probe Burying Test: For the shock-probe burying test the testing apparatus consists of a plexiglass box measuring 40x30x40 cm, evenly covered with approximately 5 cm of bedding material (odor absorbent kitty litter) with a small hole in one end through which a shock probe (6.5 cm long and 0.5 cm in diameter) is inserted. The plexiglass shock probe is helically wrapped with two copper wires through which an electric current is administered. The current is set at 2 mA. Rats are habituated to the testing apparatus for 30 min on 4 consecutive days without the shock probe in the box. On test day, rats are placed in one corner of the test chamber following drug administration. The probe is not electrified until the rat touches it with its snout or fore paws, at which point the rat receives a brief 2 mA shock. The 15 min testing period begins once the rat receives its first shock and the probe remains electrified for the remainder of the testing period. The shock elicits burying behavior by the rat. Following the first shock, the duration of time the rat spends spraying bedding material toward or over the probe with its snout or fore paws (burying behavior) is measured as well as the number of contact-induced shocks the rat receives from the probe. Known anxiolytic drugs reduce the amount of burying behavior. In addition, an index of the rat's reactivity to each shock is scored on a 4 point scale. The total time spent immobile during the 15 min testing period is used as an index of general activity. The shock-probe burying test is described in D. Treit, 1985, *supra*. The results of this test will demonstrate that Cyanoiminopipereazine Compounds are useful for treating or preventing anxiety.

5.9. Example 9: *In Vivo* Assays for Prevention or Treatment of an Addictive Disorder

The conditioned place preference test or drug self-administration test can be used to assess the ability of Cyanoiminopipereazine Compounds to attenuate the rewarding properties of known drugs of abuse.

The Conditioned Place Preference Test: The apparatus for the conditioned place preference test consists of two large compartments (45x45x30 cm) made of wood with a plexiglass front wall. These two large compartments are distinctly different. Doors at the back of each large compartment lead to a smaller box (36x18x20 cm) box made of wood, painted grey, with a ceiling of wire mesh. The two large compartments differ in terms of shading (white vs black), level of illumination (the plexiglass door of the white compartment is covered with aluminum foil except for a window of 7x7 cm), texture (the white compartment has a 3 cm thick floor board (40x40 cm) with nine equally spaced 5 cm diameter holes and the black has a wire mesh floor), and olfactory cues (saline in the white compartment and 1 mL of 10% acetic acid in the black compartment). On habituation and testing days, the doors to the small box remain open, giving the rat free access to both large compartments.

The first session that a rat is placed in the apparatus is a habituation session and entrances to the smaller grey compartment remain open giving the rat free access to both large compartments. During habituation, rats generally show no preference for either compartment. Following habituation, rats are given 6 conditioning sessions. Rats are divided into 4 groups: carrier pre-treatment + carrier (control group), Cyanoiminopipereazine Compound pre-treatment + carrier, carrier pre-treatment + morphine, Cyanoiminopipereazine Compound pre-treatment + morphine. During each conditioning session the rat is injected with one of the drug combinations and confined to one compartment for 30 min. On the following day, the rat receives a carrier + carrier treatment and is confined to the other large compartment. Each rat receives three conditioning sessions consisting of 3 drug combination-compartment and 3 carrier-compartment pairings. The order of injections and the drug/compartment pairings are counterbalanced within groups. On the test day, rats are injected prior to testing (30 min to 1 hour) with either morphine or carrier and the rat is placed in the apparatus, the doors to the grey compartment remain open and the rat is allowed to explore the entire apparatus for 20 min. The time spent in each compartment is recorded. Known drugs of abuse increase the time spent in the drug-paired compartment during the testing session. If the Cyanoiminopipereazine Compound blocks the acquisition of morphine conditioned place preference (reward), there will be no difference in time spent in each side in rats pre-treated with a Cyanoiminopipereazine Compound and the group will not be

different from the group of rats that was given carrier + carrier in both compartments. Data will be analyzed as time spent in each compartment (drug combination-paired vs carrier-paired). Generally, the experiment is repeated with a minimum of 3 doses of a Cyanoiminopipereazine Compound.

The Drug Self-Administration Test: The apparatus for the drug self-administration test is a standard commercially available operant conditioning chamber. Before drug trials begin rats are trained to press a lever for a food reward. After stable lever pressing behavior is acquired, rats are tested for acquisition of lever pressing for drug reward. Rats are implanted with chronically indwelling jugular catheters for i.v. administration of compounds and are allowed to recover for 7 days before training begins. Experimental sessions are conducted daily for 5 days in 3 hour sessions. Rats are trained to self-administer a known drug of abuse, such as morphine. Rats are then presented with two levers, an "active" lever and an "inactive" lever. Pressing of the active lever results in drug infusion on a fixed ratio 1 (FR1) schedule (*i.e.*, one lever press gives an infusion) followed by a 20 second time out period (signaled by illumination of a light above the levers). Pressing of the inactive lever results in infusion of excipient. Training continues until the total number of morphine infusions stabilizes to within ± 10% per session. Trained rats are then used to evaluate the effect of Cyanoiminopipereazine Compounds pre-treatment on drug self-administration. On test day, rats are pre-treated with a Cyanoiminopipereazine Compound or excipient and then are allowed to self-administer drug as usual. If the Cyanoiminopipereazine Compound blocks the rewarding effects of morphine, rats pre-treated with the Cyanoiminopipereazine Compound will show a lower rate of responding compared to their previous rate of responding and compared to excipient pre-treated rats. Data is analyzed as the change in number of drug infusions per testing session (number of infusions during test session – number of infusions during training session). The results will demonstrate that Cyanoiminopipereazine Compounds are useful for treating or preventing an addictive disorder.

5.10. Example 10: Functional Assay for Characterizing mGluR 1 Antagonistic Properties

Functional assays for the characterization of mGluR1 antagonistic properties are well known in the art. For example, the following procedure can be used.

cDNA encoding rat mGluR1a receptor is obtained from, *e.g.*, Prof. S. Nakanishi (Kyoto, Japan). It is transiently transfected into HEK-EBNA cells using a procedure described by Schlaeger *et al.*, *New Dev. New Appl. Anim. Cell Techn.*, Proc. ESACT Meet., 15thà (1998), 105-112 and 117-120. [Ca^{2+}] measurements are performed on mGluR1a transfected HEK-EBNA cells after incubation of the cells with Fluo-3 AM (0.5 μM final concentration) for 1 hour at 37°C followed by 4 washes with assay buffer (DMEM supplemented with Hank's salt and 20 mM HEPES. [Ca^{2+}] measurements are done using a flurometric imaging plate reader, *e.g.*, FLIPR from Molecular Devices Corporation, La Jolla, CA. 10 μM glutamate as agonist is used to evaluate the potency of the antagonists.

Increasing concentrations of antagonists are applied to the cells 5 minutes prior to application of the agonist. The inhibition (antagonists) curves are fitted with appropriate software, for example, the four-parameter logistic equation giving IC_{50} and Hill coefficient using the iterative nonlinear curve fitting software Origin from Microcal Software Inc., Northampton, MA. The results of this assay will demonstrate that Cyanoiminopipereazine Compounds bind to and modulate the activity of mGluR1.

5.11. Example 11: Binding of Cyanoiminopiperazine Compounds to VR1

Methods for assaying compounds capable of inhibiting VR1 are well known to those skilled in the art, for example, those methods disclosed in U.S. Patent No. 6,239,267 to Duckworth *et al.*; U.S. Patent No. 6,406,908 to McIntyre *et al.*; or U.S. Patent No. 6,335,180 to Julius *et al.* The results of these assays will demonstrate that Cyanoiminopiperazine Compounds bind to and modulate the activity of VR1.

Binding of Compound **DEY** to VR1: Assay Protocol

Human VR1 cloning. Human spinal cord RNA (commercially available from Clontech, Palo Alto, CA) was used. Reverse transcription was conducted on 1.0 μg total RNA using Thermoscript Reverse Transcriptase (commercially available from Invitrogen, Carlsbad, CA) and oligo dT primers as detailed in its product description. Reverse transcription reactions were incubated at 55°C for 1 h, heat-inactivated at 85°C for 5 min, and RNase H-treated at 37°C for 20 min.

Human VRl cDNA sequence was obtained by comparison of the human genomic sequence, prior to annotation, to the published rat sequence. Intron sequences were removed and flanking exonic sequences were joined to generate the hypothetical human cDNA. Primers flanking the coding region of human VR1 were designed as follows: forward primer, GAAGATCTTCGCTGGTTGCACACTGGGCCACA; and reverse primer, GAAGATCTTCGGGGACAGTGACGGTTGGATGT.

PCR of VRl was performed on one tenth of the Reverse transcription reaction mixture using Expand Long Template Polymerase and Expand Buffer 2 in a final volume of 50 μL according to the manufacturer's instructions (Roche Applied Sciences, Indianapolis, IN). After denaturation at 94°C for 2 min PCR amplification was performed for 25 cycles at 94°C for 15 sec, 58°C for 30 sec, and 68°C for 3 min followed by a final incubation at 72°C for 7 min to complete the amplification. A PCR product of ~2.8 kb was gel-isolated using a 1.0% agarose, Tris-Acetate gel containing 1.6 μg/mL of crystal violet and purified with a S.N.A.P. UV-Free Gel Purification Kit (commercially available from Invitrogen). The VR1 PCR product was cloned into the pIND/V5-His-TOPO vector (commercially available from Invitrogen) according to the manufacturer's instructions. DNA preparations, restriction enzyme digestions, and preliminary DNA sequencing were performed according to standard protocols. Full-length sequencing confirmed the identity of the human VR1.

Generation of inducible cell lines. Unless noted otherwise, cell culture reagents were purchased from Life Technologies of Rockville, MD. HEK293-EcR cells expressing the ecdysone receptor (commercially available from Invitrogen) were cultured in Growth Medium (Dulbecco's Modified Eagles Medium containing 10% fetal bovine serum (commercially available from HYCLONE, Logan, UT), lx penicillin/streptomycin, lx glutamine, 1 mM sodium pyruvate and 400 μg/mL Zeocin (commercially available from Invitrogen)). The VR1-pIND constructs were transfected into the HEK293-EcR cell line using Fugene transfection reagent (commercially available from Roche Applied Sciences, Basel, Switzerland). After 48 h, cells were transferred to Selection Medium (Growth Medium containing 300 μg/mL G418 (commercially available from Invitrogen)). Approximately 3 weeks later individual Zeocin/G418 resistant colonies were isolated and expanded. To identify functional clones, multiple colonies were plated into 96-well plates and expression was induced for 48 h using Selection Medium supplemented with 5 μM

ponasterone A ("PonA") (commercially available from Invitrogen). On the day of assay, cells were loaded with Fluo-4 (a calcium-sensitive dye that is commercially available from Molecular Probes, Eugene, OR) and CAP-mediated calcium influx was measured using a Fluorometric Imaging Plate Reader ("FLIPR") (commercially available from Molecular Devices Corp., Sunnyvale, CA) as described below. Functional clones were re-assayed, expanded, and cryopreserved.

pH-Based Assay. Two days prior to performing this assay, cells were seeded on poly-D-lysine-coated 96-well clear-bottom black plates (commercially available from Becton-Dickinson) at 75,000 cells/well in growth media containing 5 μM PonA (commercially available from Invitrogen) to induce expression. On the day of the assay, the plates were washed with 0.2 mL 1x Hank's Balanced Salt Solution (commercially available from Life Technologies) containing 1.6 mM $CaCl_2$ and 20 mM HEPES, pH 7.4 ("wash buffer"), and loaded using 0.1 mL of wash buffer containing Fluo-4 (3 μM final concentration, commercially available from Molecular Probes). After 1 h, the cells were washed twice with 0.2 mL wash buffer and resuspended in 0.05 mL 1x Hank's Balanced Salt Solution (commercially available from Life Technologies) containing 3.5 mM $CaCl_2$ and 10 mM Citrate, pH 7.4 ("assay buffer"). Plates were then transferred to a FLIPR (commercially available from Molecular Devices) for assay. Compound **DEY** was diluted in assay buffer, and 50 mL of the resultant solution were added to the cell plates and the solution monitored for two minutes. The final concentration of Compound **DEY** ranged from about 50 pM to about 3 μM. Agonist buffer (wash buffer titrated with 1N HCl to provide a solution having a pH of 5.5 when mixed 1:1 with assay buffer) (0.1 mL) was then added to each well, and the plates were incubated for 1 additional minute. Data were collected over the entire time course and analyzed using Excel and Graph Pad Prism. Compound **DEY** when assayed according to this protocol had an IC_{50} of 196.7 ± 39.8 nM (n + 3).

Capsaicin-based Assay. Two days prior to performing this assay, cells were seeded in poly-D-lysine-coated 96-well clear-bottom black plates (50,000 cells/well) in growth media containing 5 μM PonA (commercially available from Invitrogen) to induce expression. On the day of the assay, the plates were washed with 0.2 mL 1x Hank's Balanced Salt Solution (commercially available from Life Technologies) containing 1 mM $CaCl_2$ and 20 mM HEPES, pH 7.4, and cells were loaded using 0.1 mL of wash buffer containing Fluo-4

(3 μM final). After one hour, the cells were washed twice with 0.2 mL of wash buffer and resuspended in 0.1 mL of wash buffer. The plates were transferred to a FLIPR (commercially available from Molecular Devices) for assay. 50 μL of Compound **DEY** diluted with assay buffer were added to the cell plates and incubated for 2 min. The final concentration of Compound **DEY** ranged from about 50 pM to about 3 μM. Human VR1 was activated by the addition of 50 μL of capsaicin (400 nM), and the plates were incubated for an additional 3 min. Data were collected over the entire time course and analyzed using Excel and GraphPad Prism. Compound **DEY** when assayed according to this protocol had an IC_{50} of 59.4 ± 13.1 nM (n + 3).

The results of the pH-based assay and the capsaicin-based assay demonstrate that Compound **DEY**, an illustrative Cyanoiminopiperazine Compound, binds to and modulates the activity of human VR1.

The present invention is not to be limited in scope by the specific embodiments disclosed in the examples which are intended as illustrations of a few aspects of the invention and any embodiments that are functionally equivalent are within the scope of this invention. Indeed, various modifications of the invention in addition to those shown and described herein will become apparent to those skilled in the art and are intended to fall within the scope of the appended claims.

A number of references have been cited, the entire disclosures of which are incorporated herein by reference.